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# THE LUNGS IN HEART DISEASE

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THE relationship of the lungs to the heart is very close, and it is not surprising that diseases of the lung may affect the heart and diseases of the heart may affect the lungs. It is, of course, by way of the pulmonary blood vessels that this interrelationship is effected.

*Radiology of the Pulmonary Vessels.* The pulmonary arteries are readily accessible to X-ray examination. Normally most of the left middle arc of the cardiovascular shadow is formed by the main pulmonary artery. The main right and left pulmonary arteries are visible in the oblique views. The " comma-shaped " hilar shadows, lying just lateral to the bronchi, are formed almost entirely by the secondary branches of the pulmonary arteries. These give off branches, running with the bronchi. When seen end on, they form small dots. The normal lung markings are formed almost entirely by the pulmonary arteries. The veins contribute to some extent, but it is usually difficult to distinguish them from the arteries.

This normal picture is often strikingly altered in disease.

In *pulmonary plethora* there is a great increase in the pulmonary vascular shadows (Fig. 3). The left middle arc of the heart's shadow bulges conspicuously and pulsates markedly. The main intra-pulmonary (hilar) branches are also greatly widened and pulsate vigorously. The lung fields appear dense, the smaller pulmonary artery branches appear wider and darker than normal, and there is much coarse mottling produced by arteries seen end on. Pulsation is often visible in the larger of these vessels, whether seen in their length or end on, in the middle, or even in the outer, third of the lung fields (Campbell, 1951).

Pulmonary plethora is found in various forms of congenital heart disease. The commonest conditions producing it are inter-atrial septal defect, with or without anomalous drainage of one or more pulmonary veins into the right atrium; a large interventricular septal defect; patent ductus arteriosus (where the changes are usually less marked) and, among cyanotic cases, transposition of the great arteries. It is also sometimes present in Eisenmenger's complex (interventricular septal defect, dextroposition of aorta, and pulmonary hypertension). The cause of the condition is not entirely clear. Probably increased pulmonary blood flow is the most important single factor, though Campbell (1951) has pointed out that the greatly increased pulmonary blood flow produced in normal people by violent exercise does not result in the radiological picture of pulmonary plethora.

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Pulmonary plethora denotes active pulmonary congestion, and must be distinguished from the passive congestion of heart failure (see below), and from mere dilatation, with or without excessive pulsation, of the stem of the pulmonary artery, and the main intra-pulmonary (hilar) branches. This may occur with oligæmic lung fields, in cases of primary pulmonary hypertension (Figs. 4 and 5) and pulmonary stenosis with closed septa (Fig. 8).

*Pulmonary oligæmia* occurs when the pulmonary blood flow is markedly reduced, as in pulmonary stenosis. In the tetralogy of Fallot (Figs. 6 and 7) the stem of the pulmonary artery is small, so that there is a concavity, with diminished pulsation, between the aortic knuckle and the left ventricle, the hilar shadows are narrow, and the intra-pulmonary vascular markings finer and fewer than normal, with unusually translucent lung fields. In cases of pulmonary stenosis with closed septa (and without cyanosis) (Fig. 8) there is commonly post-stenotic dilatation of the main pulmonary artery, producing a marked bulge immediately below the small aortic knuckle. The dilatation may extend to the main hilar arteries, which may visibly pulsate, in spite of the low blood flow through them; but, nevertheless, the lung fields look oligæmic.

*The Bronchial Circulation.* The pulmonary artery is nutrient only to the alveolar walls, where its blood is oxygenated. The bronchi, bronchioles, alveolar ducts and some alveoli are supplied by the bronchial arteries. Blood is returned from the larger bronchi, by way of the bronchial veins, to the right atrium. In the smaller bronchi, the bronchial veins anastomose with pulmonary veins, forming venous plexuses, and the blood is returned to the left atrium. Ferguson *et al.* (1944) have shown that these anastomoses are more conspicuous in patients with mitral stenosis, and the submucous veins in the smaller bronchi become dilated and varicose. Bleeding from the veins is the commonest cause of hæmoptysis in mitral stenosis. Some of the blood enters the alveoli, where the red cells are taken up by macrophages and broken up. After many such episodes the radiological picture of hæmosiderosis is produced (see below).

Because of the blood supply through the bronchial arteries, pulmonary embolism comparatively rarely causes pulmonary infarction unless heart failure is present, and the extent of the infarct is much less than the total distribution of the occluded artery.

Capillary anastomoses between the pulmonary and bronchial circulations occur in the visceral pleura. Because of this, pleural effusions are rare in isolated right-sided failure, and though they are said to occur in isolated left-sided failure, they are commoner when both sides of the heart fail.

In cases of very severe pulmonary stenosis without patency of the ductus arteriosus, almost the only blood flowing through the lungs is that carried by the greatly dilated bronchial arteries. The normal hilar pulmonary artery shadows are missing, and in their place are irregular, tortuous, nodular shadows (Campbell and Gardner, 1950).

*Regulation of Pulmonary Circulation.* The structure of the pulmonary arteries resembles that of the systemic vessels though the walls are thinner (Brenner, 1935a). Arteries of 1·0 to 0·1 mm. in diameter have a muscular media, though it is much thinner in the pulmonary arteries than in the systemic. But the

pulmonary " arterioles," below 0·1 mm. in diameter, consist only of an endothelial tube surrounded by a single elastic fibre (Fig. 10). They differ greatly from the systemic arterioles, in which the powerful muscular walls form nearly half of the diameter, and it seems clear that their rôle in regulating blood pressure and local blood distribution cannot be so important as in the systemic circulation. The normal pulmonary artery pressure (P.A.P.) in man has been found by cardiac catheterisation to average 22/8 mm. Hg (Cournand, 1950), and the pulmonary " capillary " pressure to be 5-10 mm. Hg. The capillaries are separated only by very thin walls from the air in the air sacs, where they are exposed to a negative intrathoracic pressure of 5-10 mm. Hg. The sum of the forces tending to drive fluid through the capillary wall (capillary blood pressure + negative intrathoracic pressure) is therefore 10-20 mm. Hg, and this is opposed by the plasma colloid osmotic pressure of 25 mm. Hg. A comparatively small rise in capillary blood pressure may therefore cause fluid to exude into the alveoli. Drinker (1947) states that much fluid may be carried away by lymphatics, and this may explain why patients with severe mitral stenosis, in whom the capillary pressure at rest is often more than 25 mm. Hg, and in whom it may rise to 50 mm. Hg or more during mild exercise, do not often die of acute pulmonary œdema. The lymphatics in man, however, seem too exiguous to remove very rapidly any large quantity of fluid particularly as it has to rise, against gravity, to enter the veins in the neck, in which the pressure is likely to be raised. The most important influences on the pulmonary circulation are the output of the right ventricle and the resistance at the mitral valve, the respiratory movements and the great distensibility of the small pulmonary vessels. In many cases of inter-atrial septal defect, the pulmonary artery pressure is little raised, in spite of a great increase in blood flow, and exercise sufficient to increase the cardiac output markedly causes little or no rise in pulmonary artery pressure. This would be impossible without dilatation of the thin-walled pulmonary vessels. In isolated artificially ventilated dogs' lungs perfused at a constant rate (Brenner, 1935a), and in experimental mitral stenosis in dogs (Lasser and Loewe, 1954), a rise in left atrial or pulmonary venous pressure produced a much smaller rise in pulmonary artery pressure. Borst *et al.* (1956) found, in dogs, that a rise in P.A.P., left atrial pressure, or both, caused lowered pulmonary vascular resistance. The distensibility of the large pulmonary vessels, however, is lessened as the P.A.P. rises in mitral stenosis (Lasser and Amram, 1956).

Investigation of the effect of the autonomic nervous system, and of drugs stimulating it, upon the pulmonary circulation is very difficult, because the passive effects resulting from changes produced in the heart and the systemic circulation cannot easily be excluded. The conditions with isolated, perfused and artificially respired lungs are so abnormal that it is not surprising that conflicting results have been obtained. Investigations in man are scanty. In patients with mitral stenosis and pulmonary hypertension, hexamethonium causes a fall in pulmonary arterial pressure and, usually, also a fall in the pulmonary " capillary " pressure (Davies *et al.*, 1954; Scott *et al.*, 1955; Wade *et al.*, 1956) which cannot be explained on the basis of pulmonary arteriolar dilatation, and suggests that an important factor was lessened left atrial resistance. Fowler *et al.* (1951) found that infusion of nor-adrenaline in man caused

a rise in P.A.P. but that this was accompanied by a rise in pulmonary "capillary" pressure.

A simple method of excluding secondary effects from the systemic circulation is to investigate the effect of drugs injected into the pulmonary artery on their *first circulation* through the lungs, before they have reached the heart (via the coronary arteries) and the systemic circulation. Brenner and Berry (1938), using this method in dogs, found that adrenaline accelerated and acetylcholine slowed the blood flow through the lungs. Davison (1956) found that in patients with mitral stenosis when 10 μg. adrenaline was injected into the outflow tract of the right ventricle so that it was carried through all the pulmonary vessels of both lungs, there was an immediate rise in P.A.P., before cardiac acceleration and a rise in brachial artery pressure occurred, and that this rise in pulmonary artery pressure continued during the later rise in systemic pressure; but if the tip of the catheter through which the adrenaline was injected was advanced until it was wedged in a small branch of the pulmonary artery, so that the adrenaline traversed only a small segment of one lung, the P.A.P. did not rise till the heart accelerated and the systemic arterial pressure rose (Figs. 1 and 2). This late rise in P.A.P. is attributable to "back pressure"

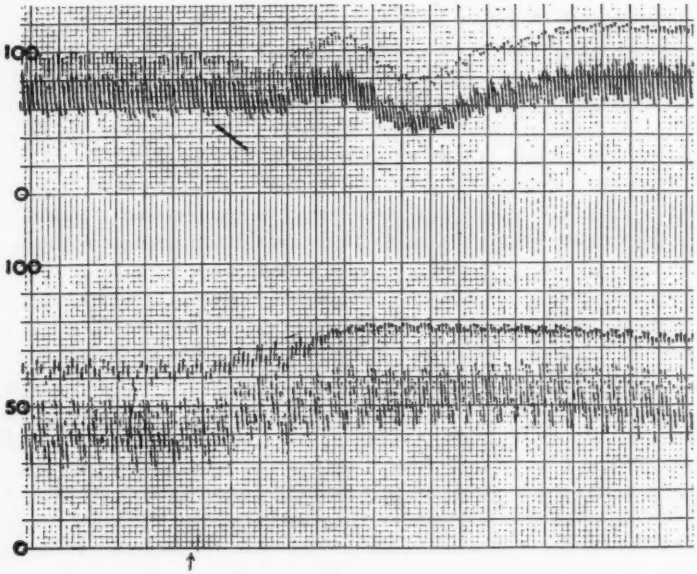


FIG. 1.—I.J., female. Mitral stenosis, with pulmonary hypertension. Upper tracing, brachial artery pressure; lower, pulmonary artery pressure. At arrow, 10 μg. adrenaline injected into outflow tract of the right ventricle. There is an almost immediate rise in P.A.P., with a simultaneous transient fall in brachial artery pressure, attributed to the immediate fall in pulmonary venous pressure when the pulmonary arterioles constrict. The rise in P.A.P. continues during the reactive rise in brachial pressure occurring when the right ventricle, contracting more forcibly in response to the raised P.A.P., restores the pulmonary venous pressure to its previous level, and during the subsequent fall in brachial pressure and cardiac acceleration produced by the entry of the adrenaline into the systemic circulation.

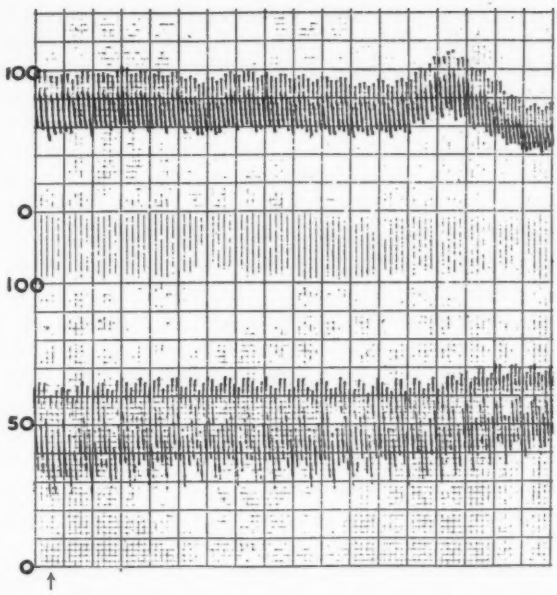


FIG. 2.—Same patient. At arrow, 10 μg. adrenaline injected through catheter wedged in small artery in the right lower lobe. No rise in P.A.P. till rise, followed by a fall, in brachial pressure and cardiac acceleration show that adrenaline has entered systemic circulation.

effects from the left side of the heart. Wood (1956) injected into the pulmonary artery a dose of acetylcholine small enough to be destroyed as it passed through the lungs, and found that this lowered the P.A.P. These findings seem sufficient to establish that the pulmonary circulation is to some extent under control of substances acting on the autonomic nervous system.

*Pulmonary Hypertension.* Although the importance of pulmonary vascular contractility is disputed, the existence of pulmonary hypertension in disease is proven. Pulmonary systolic pressures of 150 mm. Hg, that is about six to seven times the average normal, are not uncommon, a rise relatively much greater than in the most severe systemic hypertension. One of the commonest causes is mitral stenosis. Here the P.A.P. may exceed the systemic pressure, and in moderately severe cases systolic pressure of 80 mm. Hg may be found. On exercise, even though there is little rise in the cardiac output, there is a further rise in the P.A.P. This is largely a " back pressure " effect from the left side of the heart, since there is also a rise in pulmonary capillary pressure. The rise in P.A.P. is often far too high to be due only to obstruction at the mitral valve, and is often much greater than the rise in the pulmonary capillary pressure (P.C.P.). The P.C.P. at rest can rarely be above 30 mm. Hg (though higher levels have been reported), since a rise above this level would result in fatal pulmonary œdema. It has been suggested that the great rise in P.A.P. is

due to pulmonary arteriolar spasm designed to protect the pulmonary capillaries from the full force of the right ventricular pressure, a hypothesis which it is difficult to accept. Most patients with mitral stenosis who have a greatly raised P.A.P. have pulmonary arteries with narrowed lumina and thickened walls, but it seems more likely that the arteriosclerosis is the effect, rather than the cause, of hypertension. The raised P.A.P. falls greatly after a successful valvotomy. The capillary pressure also falls, but by a smaller amount. Wade *et al.* (1956) suggest that the fall in P.A.P. in such cases is due to a local reflex, not under autonomic control.

In patients with *chronic bronchitis and emphysema*, heart failure may occur during acute exacerbations of the bronchitis, when bronchial obstruction by purulent sputum increases respiratory difficulty, with anoxia and cyanosis. In such cases the P.A.P. is greatly raised, and with recovery from heart failure it falls to, or near, the normal. It has been suggested that the rise in P.A.P. is due to spasm of the pulmonary arterioles caused by anoxæmia. There is evidence that anoxæmia does cause pulmonary vascular spasm (Whitaker, 1954; Yu *et al.*, 1956), but additional factors are the permanently diminished capillary bed and the greatly increased cardiac output necessitated by the anoxæmia. Relief of anoxæmia is a particularly important part of the treatment in these cases.

In many cases of *left to right shunt*, as in patent ductus arteriosus or inter-atrial septal defect, there is an enormous increase in pulmonary blood flow with little or no rise in P.A.P., while in others, with little or no increase in blood flow, the P.A.P. is greatly raised, sometimes above the aortic, so that the shunt is reversed. In most such cases there is severe arteriosclerosis of the smaller pulmonary vessels.

*Primary pulmonary hypertension* is a condition in which the P.A.P. is raised in the absence of heart or chronic lung disease. The P.A.P. may be greater than the systemic pressure, the P.C.P. is normal, and the cardiac output is low. There must be no evidence of patency of the ductus arteriosus or cardiac septa but such evidence may be lacking even when these defects are present. The condition is commonest in children and young adults, though it has been described in old age. There is a great preponderance of females (twenty-three of twenty-five cases described in three recent papers—Shepherd *et al.*, 1957; Heath *et al.*, 1957; Evans *et al.*, 1957).

*Primary pulmonary arteriosclerosis* (Brenner, 1935b; Parmley, 1952)—*i.e.*, pulmonary arteriosclerosis associated with right ventricular hypertrophy, but without heart or chronic lung disease—is probably the pathological counterpart of this condition, though in the early cases it was not possible to measure the P.A.P.

*Pulmonary embolism* is an important cause of pulmonary hypertension. The source of the embolus is sometimes thrombus in the right auricle (Samet and Landman, 1951), but much more commonly it is thrombus formed in the leg veins of bedridden patients. Repeated, often clinically silent, pulmonary embolism in patients with severe heart failure may be the cause of lack of response to treatment. Heart failure was the primary disease in thirty-seven of sixty-two cases of pulmonary embolism described by Krause and Silverblatt (1955). Thrombus may be laid down in the pulmonary artery before and be-

hind an embolus, but primary thrombosis is probably rare. Not only clot but tumour cells, fat (Taquini *et al.*, 1956) and bilharzia ova (Girgis 1952) may cause pulmonary embolism extensive enough to cause heart failure.

Pulmonary embolism is often silent. Brenner (1935c) found old or recent emboli in thirty-six of 100 routine autopsies, and in few of these had there been any symptoms during life. Because of the bronchial artery supply to the lungs, infarcts rarely occur unless the embolus is infected or the patient has heart failure. The pulmonary arteries must be very greatly narrowed before circulatory failure occurs. The cardiac output and the P.A.P. remain normal in subjects who have had one lung removed, when at rest and even during mild exercise (Cournand, 1950; Fishman and Richards, 1956). In acute experiments in dogs the systemic arterial pressure does not fall till the cross-sectional area of the pulmonary artery stem is reduced to 14-40 per cent. of normal, and death does not follow till it is reduced to 4-16 per cent. When the stem of the pulmonary artery was constricted in dogs, which were allowed to recover, right-sided heart failure did not occur unless the cross-sectional area of the pulmonary artery was reduced to 6-12 per cent. of normal (Davis *et al.*, 1955).

Pulmonary infarction may occur when medium-sized arteries are occluded, but only if the patient has heart failure or the embolus is infected (Miller and Berry, 1951). The typical symptoms (pleuritic pain, hæmoptysis, dyspnœa, pyrexia) are not always all present, and pulmonary infarction may be clinically silent. It should be suspected when a patient with heart failure ceases to respond to treatment, or deteriorates without obvious cause. The X-ray (Short, 1951) shows irregular shadows, rarely wedge-shaped, in the periphery of the lung fields, with pleural reaction and often a small or large pleural effusion, and elevation of the diaphragm. When the hilar branches of the pulmonary artery are blocked, pulsation is diminished, but when the block is in more peripheral branches, the hilar branches may pulsate vigorously.

Embolism of small branches is common, usually symptomless, and does not cause infarction; but when the great majority of the small arteries in both lungs are blocked, either by repeated embolism or by fragmentation of a large embolus, a condition apparently identical with primary pulmonary arteriosclerosis may be produced (Muirhead *et al.*, 1952; Davison *et al.*, 1956).

*The symptoms and signs of pulmonary hypertension* are similar whether the cause is chronic lung disease, mitral stenosis, congenital heart lesions, or pulmonary embolism. The only specific symptoms of pulmonary embolism are those of pulmonary infarction, which occurs only in a minority of cases of pulmonary embolism, when the obstructed artery is not too large and not too small, and even then only if the patient has heart failure or the embolus is infected.

Complete occlusion of the main pulmonary artery or of both its branches causes instant death. With sudden, less complete occlusion there may be loss of consciousness, and sometimes several syncopal attacks in rapid succession (Brenner, 1931). There may be a crushing pain across the chest and down the arms, like that of coronary thrombosis. The patient is pale, cold, sweating, and has a low blood pressure. There is forcible pulsation in the second and third left intercostal spaces, and sometimes systolic and diastolic murmurs, occasionally with thrills. Electrocardiographic changes, resembling those of a posterior myocardial infarction with incomplete right bundle branch block, often appear

transiently (White and Brenner, 1933; Wolff, 1952). Recovery may occur, but sometimes apparent recovery is followed by the signs of chronic pulmonary hypertension, described below. The diagnosis then may be difficult because no history of an acute onset is obtained, and because the embolism may complicate a disease, such as mitral stenosis, which is capable itself of causing similar symptoms (Dimond and Jones, 1954; Magidson and Jacobson, 1955; Ball *et al.*, 1956).

Patients with severe pulmonary hypertension, unless this is suddenly produced by a large embolus, may be free of symptoms for many years. Dyspnœa is usually the first symptom, and may quickly become severe. Cyanosis, when present, is due to a low cardiac output, and desaturation of the blood in its slow passage through the tissues. Syncopal attacks, often during effort, may be an early symptom (Dressler, 1952). Pain in the chest on exertion, sometimes radiating down the arms, may occur and is indistinguishable from angina pectoris. The patient may die in an attack (Brenner, 1935b). Stuckey (1955) showed that in the attacks the electrocardiogram shows the changes of myocardial ischæmia. There may be weakness of the legs on walking, causing the patient to fall, The similarity of the symptoms to those occurring more acutely in massive pulmonary embolism is clear. The symptom complex may arise whenever the right ventricular pressure is raised (mitral stenosis, pulmonary stenosis, left to right shunts, primary pulmonary hypertension, pulmonary embolism) as well as in severe aortic stenosis, with a low, fixed cardiac and an insufficient increase, or even a diminution, in coronary and cerebral blood flow during exertion (Stuckey, 1955). Eventually the signs of right heart failure, with neck vein distension, hepatic enlargement and gross œdema, occur.

Physical examination shows a giant " a " wave in the jugular venous pulse, powerful parasternal and epigastric right ventricular pulsation, and a loud, split, palpable pulmonary second sound. The diastolic murmur of functional pulmonary incompetence may be heard, and there may be a loud pulmonary systolic murmur, occasionally with a thrill, so that a mistaken diagnosis of congenital heart disease may be made. The X-ray (Figs. 4 and 5) shows a large right ventricle, dilatation, which may be great, and often excessive pulsation, of the stem of the pulmonary artery and its hilar branches, but oligæmic lung fields. The electrocardiogram shows a tall, pointed " P pulmonale " and right ventricular preponderance.

Various *histological changes* in the pulmonary arteries have been described. The cases secondary to pulmonary embolism form a special group, though organisation of natural or experimentally produced emboli (Barnard, 1954) may result in changes difficult to distinguish from those of primary arteriosclerosis, and secondary thrombosis may occur in cases primarily arteriosclerotic. In most other cases, however, whether the cause of the pulmonary hypertension is known, as in mitral stenosis, or unknown, as in " primary pulmonary hypertension," there is a fairly constant pattern (Heath and Whitaker, 1956). The earliest change is thickening of the muscular coat of the small arteries, and the appearance of a muscular media in " arterioles," below 0·1 mm. in diameter, which normally have no muscle in their walls. This seems to be a reaction to, and not a cause of, the hypertension. The

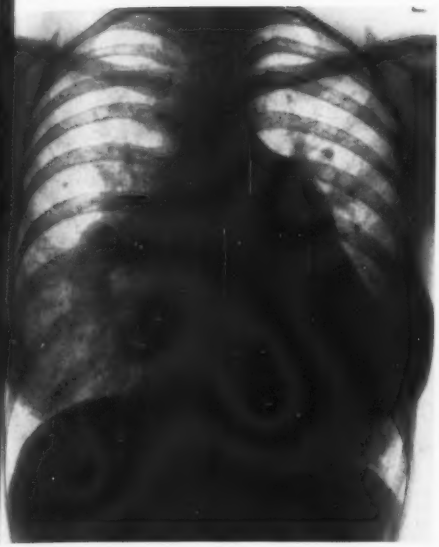

FIG. 3.—W.R., age 23, female. Inter-atrial septal defect and anomalous pulmonary venous drainage. Pulmonary plethora.

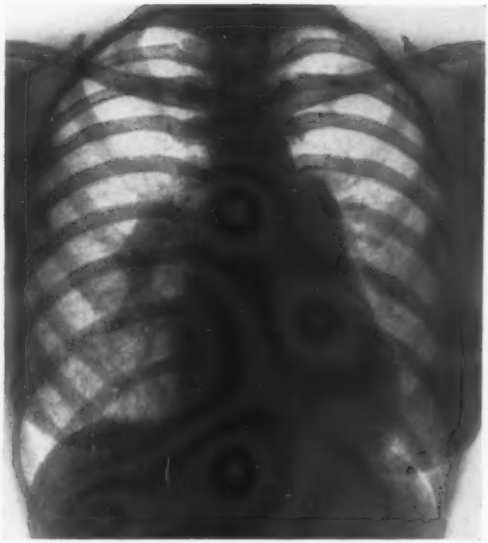

FIG. 4.—J.H., age 25, female. Primary pulmonary hypertension. The main pulmonary artery and the right hilar branch are much dilated, but the lung fields are oligaemic.

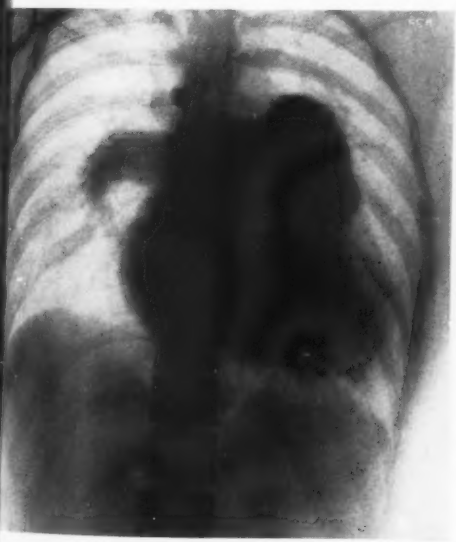

FIG. 5.—Same patient. Angiocardiogram. The dilatation of the main pulmonary artery and of its right and left branches (the latter seen end on) is well shown. The contrast medium has not filled the intrapulmonary branches.

FIG. 6.—L.C., age 33, female. Tetralogy of Fallot. There is no prominence of the left middle arc, the hilar shadow is narrow, and the lung fields oligaemic.

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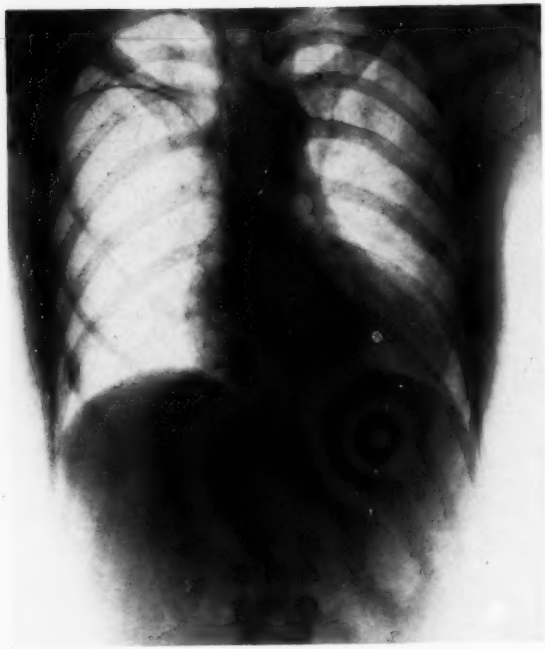

FIG. 7.—Same patient as fig. 4. Angiocardiogram. The contrast medium is in the right side of the heart, and has filled the aorta, but has not entered the pulmonary artery.

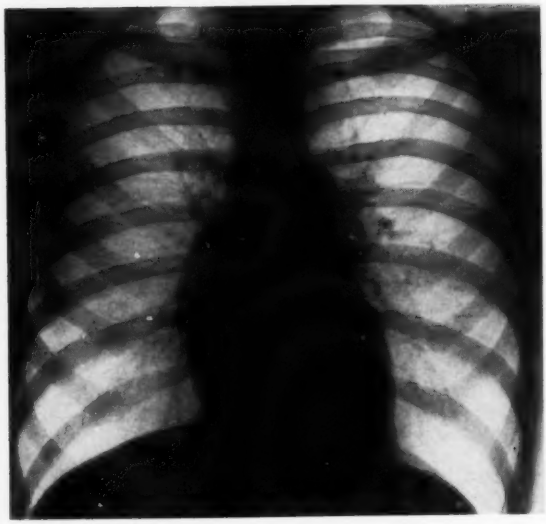

FIG. 8.—M.H., age 16, male. Pulmonary stenosis with closed septa. No cyanosis. The stem of the pulmonary artery is dilated, but the hilar shadows are small, and the lung fields oligaemic.

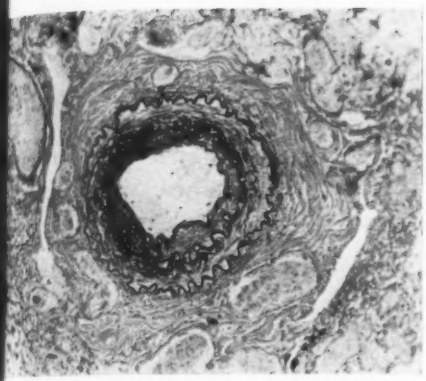

FIG. 9a.—Lung from S.A., age 23 ×135. Eisenmenger's complex. Small muscular artery, 0·25 mm. external diameter, showing thickening of the media and fibro-elastic thickening of the intima.

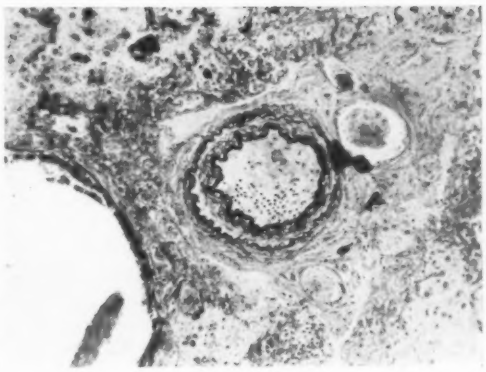

FIG. 9b.—Same case. Small muscular artery, 0·15 mm. in diameter. Lesser degree of medial thickening. Lumen almost occluded by fibrous intimal thickening.

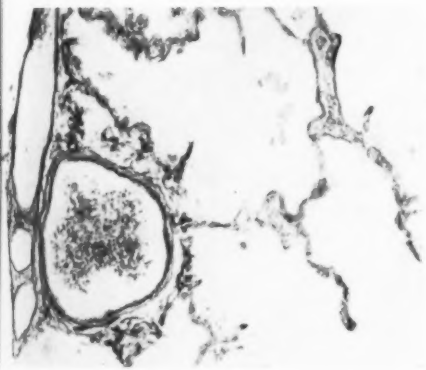

FIG. 10.—Normal lung ×150. Below and to the left is a muscular artery, approximately 0·2 mm. in diameter, with a thin muscular media between two elastic laminae. Above and to the right is an "arteriole" approximately 0·03 mm. in diameter, cut longitudinally. It consists of an endothelial tube, outside which is a single elastic fibre. It communicates with capillaries in the alveolar walls.

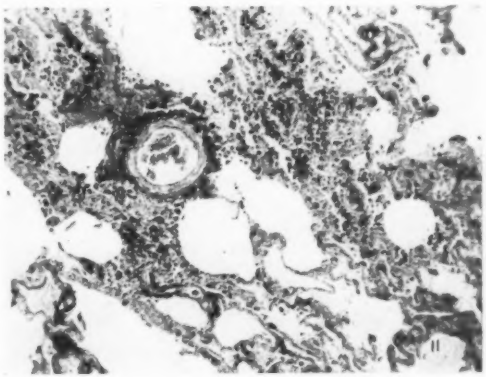

FIG. 11.—Lung from a case of mitral stenosis ×85. An artery of approximately 0·2 mm. in diameter with thick muscular walls, is above and to left of centre. Groups of alveoli are packed with haemosiderin containing histiocytes, while others are empty.

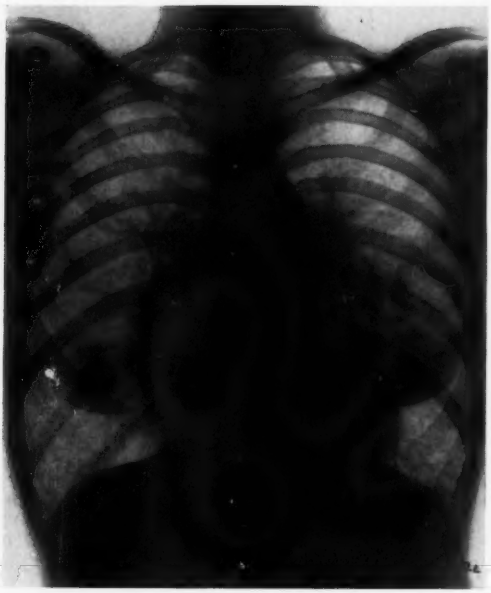

FIG. 12a.—F.L., age 39. Mitral stenosis, five days before valvotomy showing moderate pulmonary congestion, with transverse lines of oedematous interlobular septa in costo-phrenic angles.

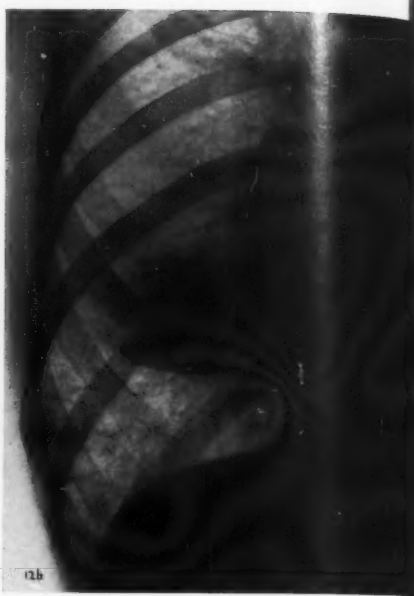

FIG. 12b.—Enlargement of 12a.

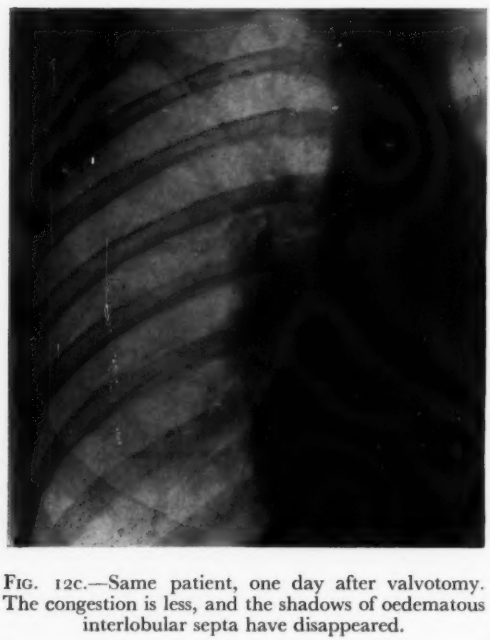

FIG. 12c.—Same patient, one day after valvotomy. The congestion is less, and the shadows of oedematous interlobular septa have disappeared.

FIG. 13.—A.D., age 41, male. Mitral stenos six months after valvotomy. Haemosiderosis a intra pulmonary calcification. Innumerable m ary shadows on a reticular background a scattered throughout the lung fields. In additi there are larger, denser, irregularly round shadows of intrapulmonary calcification.

next stage is fibro-elastic proliferation of the intima, with narrowing or even occlusion of the lumen of many small arteries (Fig. 9, a and b). This is also a reaction to the hypertension, but no doubt it also adds to it and tends to perpetuate it. In severe cases there may be necrosis of the media of small vessels (Aitchison and Richmond, 1953; Lendrum, 1956; Shepherd *et al.*, 1957; Heath *et al.*, 1957), often followed by healing, or sometimes aneurysmal dilatation of small arteries. Sometimes there are many thin-walled dilated vessels, shown by Brewer, (1955) to be anastomotic channels arising from small muscular arteries above the point where they are occluded. Heath and Whitaker (1956) attribute the necrosis to impairment of the blood supply to the arterial wall through the vasa vasorum (derived from the bronchial arteries) when the pressure in the pulmonary arteries is greater than in the systemic.

The similarity of the changes in " primary pulmonary hypertension " to those in mitral stenosis suggests that the hypertension is the cause of the arterial changes. In some cases of primary pulmonary hypertension the arterial changes are minimal, as in two of the eleven cases described by Evans *et al.* (1957), who, nevertheless, argue strongly in favour of the primacy of the arterial lesions. It has been suggested, without sufficient proof, that in cases of mitral stenosis or of left to right shunts, with great pulmonary hypertension, the fœtal type of pulmonary artery, with a thick, muscular media, persists after birth. Pulmonary artery lesions, very like those of pulmonary hypertension in man, have been produced in dogs by anastomosing the subclavian to the pulmonary artery, and so producing pulmonary hypertension (Ferguson *et al.*, 1955). This is due to increased pulmonary pressure rather than increased flow. In inter-atrial septal defect an enormously increased flow may persist into old age, with a normal P.A.P., though occasionally pulmonary hypertension develops while the patient is under observation, and pulmonary hypertension is rare in young patients with inter-atrial septal defect (Dexter, 1956). With a patent ductus, pulmonary hypertension, when present at all, is nearly always present when the patient is first seen and the pulmonary blood flow is then low. In cases with a greatly increased blood flow the P.A.P. is low, and remains low while the patient is under observation. After a successful valvotomy in patients with mitral stenosis and severe pulmonary hypertension, the fall in P.A.P. may be much greater than that in P.C.P., though the arterial lesions do not regress. Against this, however, must be mentioned the case of Edwards and Burchell (1951), in which all the pulmonary veins except that from the right lower lobe were obstructed by a fibrous mediastinal mass. The P.A.P. was 98/45. There was severe congestion, but the pulmonary arteries were normal, in the right lower lobe from which the venous outflow was not obstructed, while in all the other lobes there was no congestion but great fibrous intimal thickening and narrowing of the lumen of the small pulmonary arteries. Since all the lobes were subjected to the same P.A.P., some factor as well as pulmonary hypertension must have been involved in causing the arterial changes; but to invoke the presence of congestion only in the right lower lobe as an argument in favour of the " protective " influence of pulmonary arteriosclerosis upon the pulmonary capillaries seems scarcely fair as most of the right ventricular output must have been diverted to the only lobe from which venous outflow was not obstructed.

*The Lungs in Heart Failure.* When venous outflow from the lungs is impeded either by mitral stenosis or by left heart failure, the lungs become congested, though several authors, using dye dilution techniques, have reported that during life the pulmonary blood volume is normal or below (Rapaport *et al.*, 1956). The capillaries are dilated and tortuous, the alveolar walls thickened, and groups of alveoli are filled with fibrinous fluid and " heart failure cells " full of hæmosiderin. Neighbouring alveoli may be distended with air, due to " compensatory emphysema." The inter-lobular septa are œdematous, with distended lymphatics (Gough, 1955). The main pulmonary arteries are dilated and show atherosclerosis, and if there has been severe pulmonary hypertension the smaller branches may show marked sclerosis, with narrowing of the lumen.

Radiographically, the concavity of the middle arc of the cardiac shadow is filled in, or bulges. The hilar shadows are broad and dense and sometimes show increased pulsation, though this may be masked by a general cloudiness which obscures the margins of the arteries and the luminosity of the bronchi. The larger branches, seen end on, stand out as dense rounded shadows. In mitral stenosis with severe hypertension there may be a sudden diminution in the size, and irregularity of contour, of the peripheral arterial shadows beyond the hila (Davies *et al.*, 1953; Actis-Dato *et al.*, 1956). The lung fields, especially in the middle and lower zones, appear cloudy and less translucent than normal. Very many small vessels are visible, and can be traced to the lung margin, and there is a diffuse miliary mottling, much of which is due to small vessels seen end on, but some to groups of alveoli filled with fluid and " heart failure cells." Small or large pleural effusions are often present. Dense lines not following the distribution of the bronchi may be present, and may disappear with the relief of the heart failure. These are attributed by Kerley (1951) to distension of deep lymphatics. The interlobar fissures are often clearly seen, and as their shadows may disappear when the heart failure goes, their appearance is attributable to œdema. Short, transverse lines, are often seen in and above the costo-phrenic angle, particularly in mitral stenosis (Kerley, 1951; Short, 1955), but also in left-sided heart failure, due *e.g.* to systemic hypertension (Short, 1956). They may disappear the day after a successful valvotomy (Fig. 12, a, b, c), and are attributed to œdema of, and distension of lymphatics in, interacinar septa.

In patients with mitral stenosis, particularly with frequent hæmoptyses, and less commonly in systemic hypertension, where hæmoptysis may also occur, pulmonary *hæmosiderosis* may occur (Lendrum *et al.*, 1950; Ellman and Gee, 1951). Some of the blood from a ruptured varicose broncho-pulmonary venous anastomosis in a small bronchus is not coughed up, but enters the group of alveoli corresponding to the bronchus, where the red cells are engulfed by histiocytes, which become full of hæmosiderin granules (Fig. 11). These cells may stay in the alveoli for years. Radiologically (Fig. 13) the lung fields look dense, and there are innumerable small dense nodules, 1-2 mm. in diameter, evenly scattered. The changes of pulmonary congestion may also be present, but the hæmosiderosis persists for years, even when the congestion disappears.

Intrapulmonary *calcification* or even *ossification* may occur in patients who

FIG. 14a.—J.M., age 19, male. Chronic nephritis, B.P. 240/130. Acute pulmonary oedema. Large dense blotchy, confluent shadows spread from the hila, which are obscured. The costophrenic angles are less affected and the apices are spared.

FIG. 14b.—Same patient, after recovery from acute attack. Congestive changes are still present. The left ventricle is enlarged.

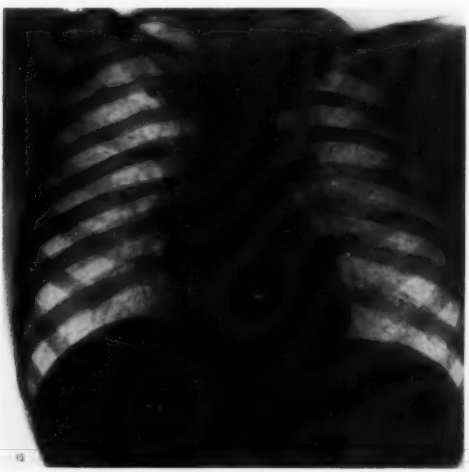

FIG. 15.—M.T., age 15, male. Cyanosis. Loud systolic murmur over upper L chest posteriorly. Pulmonary A-V aneurysm at L apex, connected by thick leash of vessels to the broad left hilar shadow. The right lung field is relatively oligaemic.

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have had heart failure due to mitral stenosis, or occasionally hypertension. The X-ray (Fig. 13) shows multiple dense, irregularly rounded shadows usually in the middle and lower zones, larger than the hæmosiderotic granules, which may also be present. The bony masses are inside groups of alveoli, and originate in small areas of organised fibrinous exudate.

Pulmonary congestion is the cause of many of the symptoms of heart failure. The lungs are more rigid, their distensibility is further reduced on exercise, and the work required for breathing, and the force which has to be exerted on the lungs to increase ventilation are much increased (Christie, 1953; Marshall *et al.*, 1954; Hayward and Knott, 1955). Saxton *et al.* (1956) found, in patients with mitral stenosis, that the distensibility of the lungs usually fell as the pulmonary " capillary " pressure rose during exercise. The maximum ventilatory capacity falls, and the ventilation required for a standard exercise increases (Stock and Kennedy, 1953) and dyspnœa quickly results. Alveolar exudate and thickened alveolar walls impede oxygenation and cause cyanosis, while capillary oozing may cause blood streaking of the sputum.

It is usually simple to distinguish the dyspnœa of heart failure from that of lung disease, though difficulties do sometimes arise. Many patients with chronic pulmonary congestion, as in mitral stenosis, have winter " bronchitis " year after year, and may not complain of dyspnœa except during the attacks, in which they have a cough with sputum, often blood-streaked. They wheeze and have many rhonchi. There is often low-grade pyrexia. The attacks often disappear after a satisfactory valvotomy. The murmur of mitral stenosis may be inconspicuous or even absent when the P.A.P. is greatly raised, and the diagnosis may then be made by the characteristic X-ray changes, and by the demonstration of a raised P.A.P. and P.C.P. by cardiac catheterisation.

The common coexistence of hypertension and chronic bronchitis and emphysema may cause doubt as to which is responsible for dyspnœa. The absence of neck vein distension and dependent œdema is no help, since these signs are absent in pure left-sided heart failure. In chronic lung disease orthopnœa is rare, and the accessory muscles of respiration in the neck are often prominent and over-active, which is not the case in heart failure.

Attacks of *cardiac asthma*, due to transient left ventricular failure, with sudden intense congestion and œdema of the lungs, must be differentiated from bronchial asthma. In both there is severe paroxysmal, often nocturnal, dyspnœa. When acute pulmonary œdema supervenes in cardiac asthma the breathing becomes agonisingly distressed, the patient is grey and sweating, moist sounds quickly spread all over the lungs, pinkish froth pours from the mouth and nose, and even if immediate treatment is available death often quickly follows. In less urgent cases, where it is possible to get a portable X-ray of the chest (Fig. 14, a and b), dense "butterfly" shadows may be seen, spreading from the hila into the lung fields, usually sparing the apices and the costophrenic angles. The shadows are not uniform, but usually consist of large, irregular, confluent blotches. The hilar structures are obscured. Pleural effusions usually are not present (Jackson, 1951). The radiological changes often disappear in a few hours (though commonly congestive changes persist), but sometimes they take several days to disappear. Occasionally the changes persist in greater or less degree for months or years, and at autopsy are

found to be due to organisation of the intra-alveolar exudate (Doniach *et al.*, 1954).

The diagnosis of cardiac from bronchial asthma is occasionally difficult especially if the attack is not seen by a doctor, and if the patient has both hypertension and bronchitis. In cardiac asthma the breathing is usually quick and panting, and the prolonged, laboured wheezing expiration of bronchial asthma is missing. Wheezing may be absent, and is always less marked than in bronchial asthma. Between attacks the X-ray changes of congestion may persist, and the pulmonary circulation time, measured by the injection of decholin intravenously, is prolonged, while in bronchial asthma it is normal or shortened.

*Pleural effusions* occur whenever pulmonary congestion is severe. Because of the anastomosis of bronchial and pulmonary vessels in the pleura, they occur chiefly when both sides of the heart fail. The effusion is rarely symmetrical but is usually greater on, and may be confined to, one side. The site of the effusion is determined by local changes in the pleura, often caused by pulmonary infarction. Usually the effusion is absorbed as the heart failure disappears, but occasionally it persists and recurs after tapping, for months or years. The heart failure need not be severe in such cases and, especially if the patient has repeated hæmoptyses, bronchial neoplasm may be suspected.

*Pulmonary arteriovenous fistula*, though rare, is important as it may be cured surgically (Brink, 1950; Burchell and Claggett, 1947; Ronald, 1954). The lesions may be multiple and there are often telangiectases in the skin and mucous membranes. If the fistula is large the patient is deeply cyanosed and has polycythæmia and clubbing of the fingers and toes. A continuous murmur may be heard over a superficial lesion. The X-ray (Fig. 15) shows a nodular shadow, sometimes pulsatile, attached by a thick leash of vessels to an enlarged, vigorously pulsating hilar shadow. The rest of the lung fields is often somewhat oligæmic. Occasionally, large communications between bronchial and pulmonary arteries occur (Claiborne and Hopkins, 1956). There is then no cyanosis even if, as sometimes happens, there is also a communication with a pulmonary vein.

## Summary

1. The X-ray appearances of the pulmonary vessels in health, and the changes produced when the pulmonary blood flow is greatly increased (pulmonary plethora), or greatly reduced (pulmonary oligæmia), are briefly described.

2. The chief nutrient vessels to the lungs are the bronchial arteries. Because of this pulmonary embolism is much commoner than infarction. The greatly dilated bronchial arteries may have an important respiratory function in cyanotic congenital heart disease with severe pulmonary stenosis. Rupture of pulmonary-bronchial venous anastomoses in the mucosa of small bronchi is the chief cause of hæmoptysis in mitral stenosis.

3. The pulmonary circulation largely follows passively changes in the right ventricular output and left auricular resistance. The importance and even the existence of vasomotor control is disputed. Evidence of its existence is adduced.

4. A great rise in pulmonary artery pressure may occur in mitral stenosis, left-sided heart failure, chronic lung disease, some cases of congenital heart disease with left to right shunts, massive pulmonary embolism, and occasionally where no cause is found (" primary pulmonary hypertension "). The small pulmonary arteries are thickened and narrowed. These changes are thought to be the effect rather than the cause of the hypertension, though once present they help to perpetuate it. Among the symptoms of pulmonary hypertension are syncope during effort, anginal pain and great weakness of the legs. The physical signs, X-ray and electrocardiographic appearances by which it can be recognised are briefly described.

5. Pulmonary capillary hypertension, with congestion and œdema of the lungs, occurs in mitral stenosis and left heart failure. The symptoms and X-ray appearances are briefly described.

I am greatly indebted to my colleagues J. C. B. Bishop and F. H. Haworth for the X-ray photographs, P. H. Davison for the pressure records, and D. Heath for the photo-micrographs.

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# SOME ASPECTS OF THE PULMONARY CIRCULATION

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Our knowledge of the topography of the small pulmonary vessels is still imperfect, being based on histological patterns and on vascular models, which do not give adequate information about the smaller vascular pathways.

Recently new radiographic techniques have been described, and microangiography appears to have a wide future from this point of view. The work of Barclay and his associates (1944) has shown the method and its great possibilities. A paper by Sousa and Mirabeau Cruz (1955) has reported the use of microradiographic technique in the study of the fine hepatic circulation. In the present paper studies of the pulmonary circulation by the same method are described.

## Methods

The technique was applied both to dogs and to human material:

A. Experiments were made on dogs in which radio-opaque material was injected into the pulmonary vessels, both *in vivo* and post-mortem.

1. Thorotrast was injected into the pulmonary artery, using the normal blood flow to fill the vascular tree which was completed after ligature of the pulmonary veins. The lung was then removed, moderately distended, and the bronchus ligated.

2. The lung was removed and perfused with physiological saline, thoroughly washing out the vascular tree; then diagnothorine was injected into either the artery or the veins. This method was also used on pulmonary lobes showing collapse.

B. Similar experiments were made on human lungs removed surgically for advanced tuberculous lesions or hydatid cysts. The contrast material was injected after prolonged perfusion with physiological heparinised serum.

The lungs were fixed in formol or alcohol at 95°C., and 100 $\mu$ thick sections were cut after freezing. These sections, mounted on stylofern slides, were radiographed with the same apparatus used in previous studies on the liver.

## Results

Small branches of the pulmonary artery were seen to spread to the parenchyma and also to the walls of the bronchioli (Fig. 1). Pulmonary veins, receiving venules which drained alveolar capillaries, were seen in the septa (Fig. 2).

At the periphery of the lung the pulmonary arterioles gave rise to large capillaries, named " giant capillaries " by von Hayek (1953) (Fig. 3); these capillaries connected with venules which drained into interlobular veins.

In both the human and the dog specimens preferential channels were seen

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around the limits of the alveoli giving rise to the true capillaries (Fig. 4). In collapsed lung the true capillaries were not perfused by the radio-opaque material, the venous plexus of the bronchial wall being abundantly injected—sufficiently so to be obvious macroscopically (Fig. 5).

In human lungs a number of arteriovenous anastomoses were seen. Some were short and tortuous (Fig. 6), like the *sperrarterien* described by von Hayek (1953); others were longer and ran straight (Fig. 7); finally, others were placed within the parenchyma and supplied the capillary network (Fig. 8). These anastomoses were not seen in the lungs of dogs, probably owing to the small number of specimens examined.

## Discussion

It is considered that micro-radiography is an excellent method for studying the finer vascular pattern from both the anatomical and functional points of view.

In collapsed lung the capillary network is blocked, the radio-opaque material flowing into the bronchial venous system. This observation might be related to the explanation of the hæmoptyses which occur in bronchiectasis and bronchial tuberculosis.

The existence of pulmonary arteriovenous anastomoses in normal lung has been indicated previously by other techniques. Glass spheres up to 500 $\mu$ in diameter pass through the pulmonary vascular bed of both human lungs studied at necropsy (Tobin and Zariquiey, 1950), and in experimental animals (including dogs) at necropsy (Prinzmetal *et al.*, 1948) and *in vivo* (Niden and Aviado, 1956). The anastomoses have been demonstrated by cinefluorography in living dogs by Rahn, Stroud and Tobin (1952).

The anatomy of the vessels has been studied by the cast technique by Tobin and Zariquiey (1950) in man, who found the larger shunts at the apices of the lobular subdivisions, with smaller shunts in smaller units and in the pleura. Apart from the *sperrarterien* of von Hayek (1953), which this study suggests is only one of the structural types of anastomoses, their histology has received scant attention.

Recently, the functional regulation of these shunts has been studied in dogs (Niden and Aviado, 1956; Williams; 1956), but results are conflicting. The factors concerned may well be related to those operative in arterio-venous shunts elsewhere in the body, such as those which were examined in the intestinal mesentery by Chambers and Zweifach (1944).

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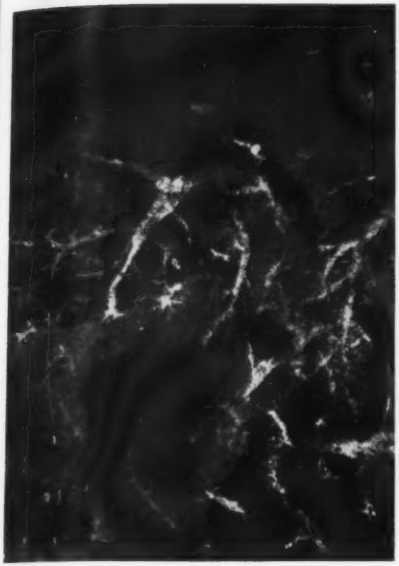

FIG. 1.—Pulmonary arterial branches spreading to the walls of the bronchioli and to the parenchyma. (×30)

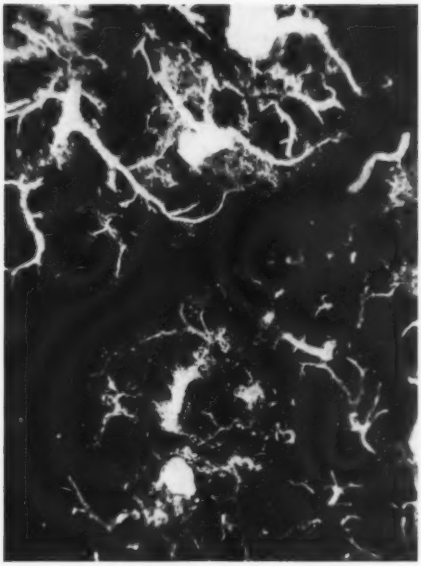

FIG. 2.—Endings of the pulmonary artery at the level of the interlobular septum. (×30)

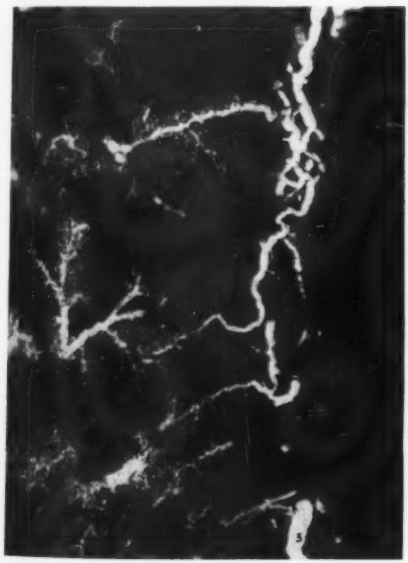

FIG. 3.—Giant sub-pleural capillaries. (×60)

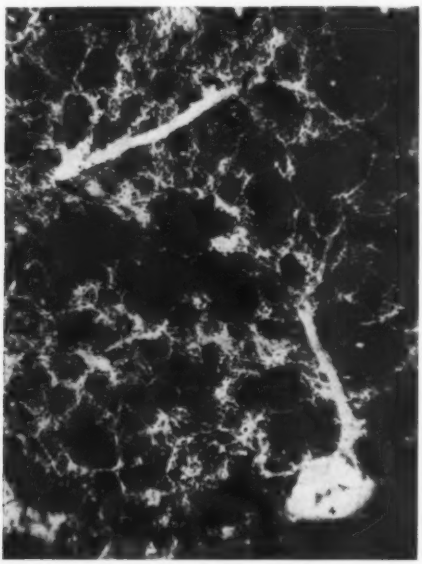

FIG. 4.—Original picture of the true pulmonary capillaries.

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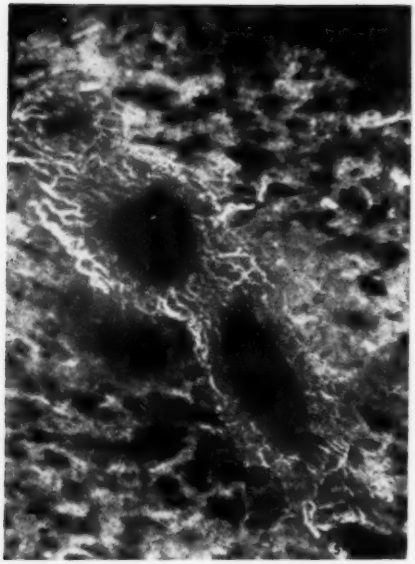

FIG. 5.—Venous plexus of the bronchial wall. (×45)

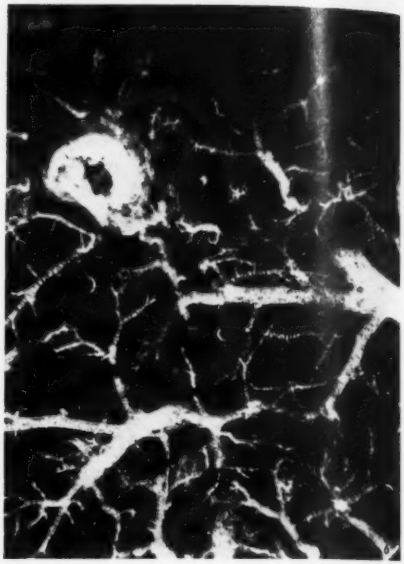

FIG. 6.—Short and tortuous arterio-venous anastomosis belonging to the type of the "Sperrarterien" described by von Hayek. (×60)

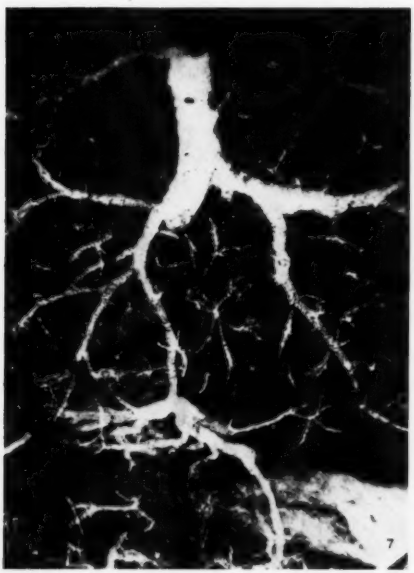

FIG. 7.—Long and straight arterio-venous anastomosis. (×60)

FIG. 8.—Arterio-venous anastomosis placed in the depth of the parenchyma and supplying pulmonary capillaries. (×60)

# PHYSIOLOGICAL PRINCIPLES IN THE MANAGEMENT OF PULMONARY EMPHYSEMA*

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We have little or no control over the structural abnormalities which occur in the lungs in emphysema, but it is possible within limits to rectify some of the disturbances of function which arise from this disordered structure. It is the purpose of this brief review to consider the principles and methods with which this can be achieved.

There are many ways in which the respiratory function of the lungs can be altered. In the case of emphysema, the abnormalities of function are multiple and vary in nature and degree throughout the course of the disease. Since the management of patients with emphysema depends greatly on the assessment of these abnormalities, we shall present first a brief description of the alterations in respiratory function in emphysema and of their evolution during the advance of the disease.

## Physiological Background

The distension of the emphysematous lung which is its most obvious characteristic is readily measured in life as an increased residual volume, and this is accompanied by a diminution in the vital capacity (Baldwin *et al.*, 1948-49). These quasi-anatomical measurements are an expression of a change in the mechanical properties of the lungs. There are two chief elements to this change. First, the lungs lose their power of elastic recoil. Secondly, there is often an abnormal narrowing of the bronchi. The narrowing may be due to spasm, to mucosal thickening and fibrosis in the walls, or to the external force resulting from an increased pressure in the surrounding alveoli. Whatever its cause, it becomes more apparent during expiration than in inspiration, as can be shown by recordings on a spirograph.

Distension of the lungs alters the position of the ribs and diaphragm in a way which renders the bellows action of the chest less effectual. The ventilatory capacity, however, is diminished to a more important degree by the increased resistance to flow of air through narrowed bronchi. Thus, in emphysema, there is a characteristic reduction in the maximum breathing capacity, which is the maximum volume of air that the patient can breathe in and out during a short measured period of time.

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A more subtle but no less important disturbance of ventilation is the inequality of distribution of the inspired air to the alveoli. Such uneven ventilation of the lungs can be measured by means of nitrogen wash-out or helium-mixing curves (Darling *et al.*, 1944; Bates and Christie, 1950; Briscoe *et al.*, 1951; Fowler *et al.*, 1952). The uneven distribution of ventilation is most probably accompanied by an uneven distribution of the flow of blood through the lungs. Thus the ratio of ventilation to perfusion in each alveolus may vary greatly throughout the lung.

If the ratio of ventilation to perfusion in any alveolus is abnormally low, then the blood that it sends to the pulmonary veins will contain less oxygen and more $CO_2$ than it normally would. Thus, in the extreme instance, where there is no alveolar ventilation, the pressures of the gases in the alveolus will approximate to those in the mixed venous blood, and the blood passing through the alveolar capillaries is unchanged. Where the ratio of ventilation to perfusion is abnormally high, an excessive quantity of $CO_2$ is removed from the blood in the alveolar capillaries and thus the blood leaving the alveolus has a low $CO_2$ content. On the other hand, hyperventilation can cause very little increase in the oxygen content of blood leaving the alveolus, since under normal conditions this blood is in any case as much as 98 per cent. saturated with oxygen. This difference in the effect of hyperventilation on the content of oxygen and $CO_2$ in arterial blood arises out of the difference in shape between the dissociation curves for these two gases. It has an important practical bearing. It means that, if one portion of the lung is hypoventilated with respect to its perfusion, then hyperventilation of the rest of the lung can correct the level of $CO_2$ in mixed arterial blood but cannot correct the lowered arterial oxygen saturation to the same extent.

Thus the first abnormality of the arterial blood in emphysema is a decreased oxygen saturation. At that time the stimulation of the respiratory centre by the slightest retention of the $CO_2$ will increase the total ventilation sufficiently to hyperventilate some portions of the lungs and thus restore the partial pressure of $CO_2$ in the arterial blood ($Pa_{CO_2}$) to a normal level. It has been noted, however, that the ventilatory capacity of the lungs becomes progressively diminished in emphysema. A time is therefore reached in the evolution of the disease when the patient is no longer able to compensate for an increasing maldistribution of air and blood in the lungs by increasing the total ventilation. At this time he begins to accumulate $CO_2$ in the body. At first this will occur only during exercise when the production of $CO_2$ by the body is increased, but eventually it remains even while resting (Baldwin *et al.*, 1949).

Under normal conditions, the level of $Pa_{CO_2}$ is regulated most delicately by its own stimulating action on the respiratory centre. Thus the $Pa_{CO_2}$ controls the activity of the respiratory centre which controls the degree of activity of the respiratory muscles which controls the level of ventilation which controls the elimination of $CO_2$ which controls the $Pa_{CO_2}$. Emphysema disturbs this self-regulatory cycle at several points. First, by increasing the variation in ventilation: perfusion ratios throughout the lungs, it increases the level of total ventilation required to maintain the $Pa_{CO_2}$ at a normal figure. Secondly, it makes the lungs resistant to ventilatory movement so that the same amount of work on the part of the respiratory muscles leads to less

ventilation of the lungs. To some extent the increased muscular work of breathing must also increase the production of $CO_2$ in the body. It is the combination of these factors which eventually causes the retention of $CO_2$ in the body. Chronic retention of $CO_2$ leads to an increase in the alkali reserve and this in itself may lower the response of the respiratory centre to sudden increments of $CO_2$ retention (Scott, 1920). Finally, there is the possibility that the sensitivity of the respiratory centre in patients with emphysema and chronic $CO_2$ retention is intrinsically impaired (Fishman *et al.*, 1955).

Carbon dioxide is a narcotic gas. Its retention in the body in increasing amounts causes drowsiness which passes into coma and death. This is the cause of death of many patients with emphysema. The measurement of the $Pa_{CO_2}$ is therefore of great value in the management of emphysema. It is of no less necessity than the measurement of the blood urea in chronic nephritis.

Another factor influencing the exchange of gases in the lungs is the impairment of the diffusing capacity across the alveolo-capillary membrane which is found to a certain extent in emphysema. This further decreases the oxygen saturation of arterial blood but does not influence the exchange of $CO_2$ because this gas is so highly transmissible.

As the oxygen saturation of the blood declines, a compensatory polycythemia occurs, probably due to a lowered tension of oxygen in the blood perfusing the bone marrow. Hence, there is a rise in the hæmatocrit and an increased total blood volume due to the increase in red cells, although this is not as a rule accompanied by a comparable increase in the content of hæmoglobin. During the evolution of the disease there is also a rise in the pressure in the pulmonary artery. There may be several reasons for this pulmonary hypertension—the anatomical diminution in the size of the pulmonary capillary bed, the increased viscosity of polycythemic blood, an increased pulmonary blood volume and the increase in pulmonary vascular resistance and in cardiac output stimulated by hypoxia (Harvey *et al.*, 1951; Fishman *et al.*, 1952). Eventually, the increased load on the right ventricle together with its impaired supply of oxygen cause it to fail.

## Application to Treatment

Although the preceding discussion has treated the evolution of the physiological abnormalities in emphysema as a continuous process, this is most often in reality far from true. The natural history of the disease is usually influenced greatly by attacks of respiratory infection which temporarily exacerbate the physiological abnormalities. Indeed, it is this episodic nature of the course of the disease which affords the physician his greatest opportunity to be of use by sustaining the patient during the time when his life is acutely in danger.

The control or prevention of such respiratory infections is therefore of basic importance in therapy. Very often a simple attack of coryza will be the start of an extremely grave situation and patients who are liable to such exacerbations should be very seriously advised to go to bed and take antibiotics each time they catch a cold. Antibiotics also play an important rôle in the suppression of more chronic bronchial infections.

However, the scope of this discussion has been limited primarily to the

correction of physiological abnormalities. From a therapeutic point of view these abnormalities may be considered under three headings—$CO_2$ retention, hypoxia and right ventricular failure.

*$CO_2$ Retention*

Since retention of $CO_2$ in the body comes about because of an inadequate ventilation of the alveoli, the main object of therapy is to increase alveolar ventilation. To some extent this can be achieved by the inhalation of bronchodilator sprays (whether these act by decreasing spasm or "decongesting" mucous membrane). Advice against smoking will often be equally important. It is possible, also, that breathing exercises can help in this respect. Lastly, in recent years, mechanical hyperventilators have been found to be of great value (Boutourline-Young and Whittenberger, 1951). These are of two main types. In the first type the patient breathes through a tight-fitting face mask and controls the rate of ventilation himself. As he begins to breathe in, a trigger mechanism releases air from a compressed-air cylinder at an adjustable pressure which is higher than atmospheric. In this way the flow of air during inspiration can be greatly augmented. As soon as the patient starts to breathe out, the flow of air from the cylinder is automatically cut off (Motley *et al.*, 1947). The convenience and mobility of such hyperventilators has made them of great use not only in the wards but also in the outpatient clinic and occasionally in the patient's home. Most patients learn to control these intermittent positive pressure machines very rapidly. However, the presence of severe $CO_2$ retention causes drowsiness, inattention and often confusion. Under these circumstances active co-operation from the patient may become impossible and recourse has to be made to the more powerful mechanical ventilators such as the Drinker respirator, or the more recently developed cuirasse-type respirators, although even here, of course, the patient has to be taught not to fight against the machine.

What method of increasing alveolar ventilation is used will depend on the severity of the $CO_2$ retention. In cases with a mild tendency to $CO_2$ retention at rest, or more particularly during exercise, the use of bronchodilators alone may be sufficient. Where there is chronic retention of $CO_2$ of some severity ($Pa_{CO_2}$ over 50 mm. Hg; normal, 38-42 mm. Hg) mechanical hyperventilation by means of a mask for two to three hours each day will be of help. Such hyperventilation will also be necessary in cases of acute $CO_2$ retention due to respiratory infection. It is here, however, that the Drinker respirator or its equivalent often has to be used. In such cases mechanical ventilation has to be maintained for eighteen to twenty hours a day to begin with, the length of time being gradually decreased day by day according to the results from serial arterial blood analyses. Usually the Drinker respirator is not needed beyond ten to fifteen days. The task of nursing these patients is no easy one. They are difficult psychologically and incapacitated physically, while to these are added all the problems of feeding, drinking and excreting in a closed respirator.

In some instances it may be beneficial to carry out a tracheotomy in such patients who require intensive mechanical hyperventilation. This procedure

reduces the volume of the respiratory dead-space and thus improves the effectiveness of the ventilation of the alveoli. It also provides an opportunity to suck out by means of a rubber catheter the viscid secretions which often accumulate in the bronchial tree and which the patient may find it impossible to expectorate.

Another approach to the problem of elimination of $CO_2$ has been the use of "Diamox," a carbonic anhydrase inhibitor (Fishman *et al.*, 1955). When the $Pa_{CO_2}$ rises, there is an increase in alkali reserve mediated by the kidneys. "Diamox" greatly increases the loss of bicarbonate in the urine and thus lowers the alkali reserve. Subsequently the $Pa_{CO_2}$ falls. The mechanism whereby this fall in $Pa_{CO_2}$ happens is not certain, but possibly there is some small increase in ventilation resulting from the acidosis associated with the fall in alkali reserve (Galdston, 1955). The arterial oxygen tension ($Pa_{O_2}$) is caused to rise and this may simply be due to the physical effects of a lowered concentration of $CO_2$ in the alveolar gas. Whatever the mechanisms, the final effects of the drug are frequently beneficial. "Diamox" is not only of use in acute retention of $CO_2$. It has been found valuable in some cases when given for one to two years in a dosage of 0·5 gm. daily to patients with severe chronic $CO_2$ retention (Fishman *et al.*, 1955). One rewarding result of this therapy has been that the patients feel mentally brighter and more alert, presumably a consequence of the lowered $Pa_{CO_2}$. There is, however, some danger of renal calculi when the drug is given over such prolonged periods.

In the management of patients with $CO_2$ retention, it will be evident that anything which reduces the activity of the respiratory centre will be harmful. Thus it is important not to administer those hypnotic drugs which are respiratory depressants. Unfortunately, these patients are often confused and some form of sedation may be necessary. Under these circumstances chloral or paraldehyde seem to be best, while barbiturates and morphine derivatives are greatly to be avoided.

*Hypoxia*

At first sight it would seem that the correction of hypoxia could be very simply effected by the administration of oxygen. Unfortunately, however, the administration of high concentrations of oxygen in patients with emphysema may itself cause a dangerous fall in ventilation. (Richards *et al.*, 1934). Hypoxæmia is a respiratory stimulant, acting on the respiratory centre via the chemoreceptors of the carotid body and aortic arch. Although the respiratory stimulus due to hypoxæmia is very much less than that due to hypercarbia, it may still be sufficient to be of vital importance in patients with emphysema and $CO_2$ retention. Thus, when these patients breathe a high concentration of oxygen, the $Pa_{O_2}$ rises. This reduces the activity of the respiratory centre and therefore lowers a ventilation which was already inadequate. In this way the $Pa_{CO_2}$ rises still further. The level of $Pa_{CO_2}$ is in fact of far greater importance than the level of $Pa_{O_2}$. A patient with congenital cyanotic heart disease, for instance, may maintain normal metabolism at a very low $Pa_{O_2}$ for many years, while the narcotic effects of $CO_2$ retention are very soon felt.

The simple administration of oxygen to a patient with emphysema and $CO_2$ retention will often be sufficient to cause coma. If oxygen is deemed necessary, it should therefore only be given while the patient's ventilation is being controlled by a mechanical ventilator such as the Drinker.

*Heart Failure*

The treatment of heart failure due to emphysema is little different from the treatment of congestive heart failure from any other cause. Its chief components are therefore rest, digitalis, a low-sodium diet, mercurial diuretics and phlebotomy. In addition there are those measures which are taken primarily to rectify the respiratory disorder.

Although the cardiac output of these patients is usually higher than normal, it is still inadequate to meet the increased requirements imposed by the disease. This is shown by the acute effects of giving digitalis. During the first hour following the injection of the drug there is an increase in cardiac output associated with a decrease in the end-diastolic pressure in the right ventricle (Ferrer *et al.*, 1950). These effects we believe to be due to an increased efficiency of the right ventricular myocardium. Two to four weeks after the failure has been treated, the output of the heart will have returned towards a normal level (Ferrer *et al.*, 1950). And this we believe to be due to a withdrawal of those excessive demands on cardiac output which had developed during the acute exacerbation from factors such as fever, hypoxia, hypervolæmia and increased work of breathing.

An acute result of giving digitalis may be a rise of a few mm. Hg in the pressure in the pulmonary artery. Such a rise is too slight to add substantially to the burden of the right ventricle and in any case it presumably arises out of an increase in right ventricular output. Measurements taken two to four weeks after the initiation of therapy, however, have shown great reductions in the pulmonary arterial pressure, often to within the normal range (Ferrer *et al.*, 1950).

Digitalis is therefore a most beneficial drug in these patients. In addition, a low-sodium diet and mercurial diuretics will oppose the accumulation of saline in the extra-cellular spaces. Diamox also has a diuretic action in conjunction with its effect on $CO_2$ metabolism. Finally, phlebotomies may be used to diminish the blood volume and more especially to reduce polycythemia.

In these patients rest is doubly necessary. It not only lessens the burden on the heart directly but it also decreases the requirements for gaseous exchange in the lungs. Similarly, after the patient has recovered from the acute attack the restriction of exercise serves a dual purpose. With the same ends in view, some physicians have even advised producing a mild myxoedema by means of anti-thyroid drugs.

*Prolonged Management*

The treatment of congestive failure or acute $CO_2$ retention is not an end in itself. When the patient has left the hospital, periodic attendance at a clinic where facilities for respiratory investigations are available is most valuable for preventing further relapses from going too far or for managing chronic

$CO_2$ retention. The continued care of these patients has other rewards; for there are few with this chronic, incurable and so often neglected disability who are not grateful for the sense of security given by such a permanent source of interest and understanding.

## Summary

In emphysema a combination of wide variation in alveolar ventilation: perfusion ratios and an over-all reduction in ventilatory capacity leads to hypoxæmia and hypercapnia. Hypercapnia is a common cause of death; it can be reduced by improving the alveolar ventilation in various ways and in some instances by giving " Diamox." When congestive heart failure occurs its treatment is basically the same as that of congestive failure from any other cause.

There is no cure for this illness and very little that can be offered most patients with mild or moderate emphysema who come complaining of shortness of breath and in whom the blood gases are normal. But within the small area of physiological abnormalities considered here, a certain amount can be done to prolong life and alleviate distress.

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# CHRONIC BRONCHITIS IN THE AGED

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Chronic bronchitis has now become the most important disease affecting the respiratory organs. It kills more people than pulmonary tuberculosis, pneumonia or carcinoma of the bronchus. As a cause of absence from work it has become a national problem. Among the older section of the population, it accounts for some twenty thousand deaths a year, being surpassed only by cardiac disease, cerebral vascular accidents and cancer as a lethal agent. Since the care of old people has now become recognised as a priority in the National Health Service, chronic bronchitis must be regarded as an important public enemy.

## Incidence

In general practice, respiratory infections among elderly people bulk large, especially during winter months. Fry (1954) gives an incidence of 142 per thousand men aged 60 to 69 and 90 per thousand for women of similar age. Men older than this show a figure of 125 per thousand, while older women rise to 127 per thousand. Such figures are double those of any previous decade. The records of the Registrar-General suggest a high plateau between 65 and 75, with the death rate in the 80s equalling that in the later 50s. In a series of necropsies in a general municipal hospital, Piggott found that 43 per cent. of those dying from chronic bronchitis were over 70 years old. His 2,221 aged subjects (Howell and Piggott, 1949) showed that out of 245 subjects over 80, some 11·4 per cent. showed evidence of chronic bronchitis. Below this age, men outnumbered women by two to one. In the 80s and 90s, however, women preponderated. Among twelve nonagenarians whose diagnosis was confirmed at necropsy, only the four youngest were male. These facts dispute the verdict of Oswald (1953), who calls chronic bronchitis " a disease of middle-aged men." His series of 1,000 cases, chiefly from the Brompton and St. Bartholomew's Hospitals, contained only 27 patients over the age of 70.

## Ætiology

It is generally agreed that previous respiratory infections predispose to chronic bronchitis. Oswald mentions past bronchitis and pneumonia. In my own series, pulmonary tuberculosis had been present in some 10 per cent. of the cases. It is interesting to note that, among the 300 subjects coming to necropsy, 10 per cent. had apical scars and another 10 per cent. showed fibrosis in the upper lobes.

Climatic conditions are known to affect chronic bronchitis. Fog is the most serious enemy. Next, a combination of cold and wet is dangerous to the aged,

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according to my experience with Chelsea pensioners. A spell of four or five cold, wet days was followed by an increase in admissions to the Infirmary of bronchitic patients. Fog, however, was much quicker in its effect, increasing the admissions within two days.

Smoking is known to influence chronic bronchitis, but there is one clinical group of very old women in which it is not a factor. These patients manifest the degenerative changes in their respiratory tract which were described by Macklin and Macklin (1942).

## Pathology

The basic pathology of chronic bronchitis has been well described by Reid (1954). She stresses the proliferation of mucus glands, œdema of the bronchial wall and infiltration with round cells. Prominence is also given to the changes of exudate, œdema, alveolar collapse and emphysema in the terminal parts of the air passages.

Elderly patients often show emphysematous lungs which are congested. The state of the epithelium varies from place to place. One area may retain columnar ciliated cells; another has only low, flatter cells; while elsewhere the basement membrane is bare. Patches suggestive of hæmorrhage may be seen, while marked fibrosis is very common. Some sections may indicate a fair amount of muscle, while others show little or none. Extensive proliferation of glands full of mucin is usually present. The older subjects often have calcification of the bronchial cartilage. Those over the age of 80 normally show atrophic, not hypertrophic, emphysema. Some thickening may be seen in the walls of the larger arteries. Marked black pigmentation often occurs. It is noteworthy that very old subjects without bronchitis present a normal histological picture of the bronchi apart from arterial thickening and calcification of cartilage even at 100 years old.

It must always be remembered that old people are the seat of multiple pathology, among which the chest infection may only be a minor incident. For example, F.E., aged 78, had atheromatous great vessels, a calcified aortic valve, fibroid scars in the left ventricle, pericardial adhesions, a carcinoma of the stomach and sclerotic kidneys. Other cases died of such lesions as carcinoma of the prostate, cerebral thrombosis, coronary occlusion, pyelonephritis, cerebral hæmorrhage, ruptured right ventricle, carcinoma of the bladder, pancreatitis, and so on, when chronic bronchitis was the main presenting lesion.

## Clinical Aspects

In old age, winter bronchitis with a slow recovery may be either a regular feature or an occasional incident. Some men who start with an incidental bronchitis gradually drift into the chronic form of the disease. Others, though subject to a "weak chest," develop no further. When the condition becomes established, it may present several patterns. One group of patients shows a predominantly infective picture, with exacerbations of pyrexia from time to time. A second group has wheezing as the presenting symptom. In a third, much smaller class, poor respiratory function due to advanced emphysema preponderates over everything else.

As examples of these types we may quote the following cases:

(1) F.H., who had been a regular bronchitic for years, developed periodic acute episodes from time to time. These would begin with a rise of respiration rate, with a rise in the pulse rate as the amount of sputum increased. Eventually, the temperature would be raised with a clinical picture of acute bronchitis. Repeated X-ray examinations revealed that pulmonary consolidation began at the time that the respiration rate increased. The advent of pyrexia coincided with radiological evidence of well-marked broncho-pneumonia.

(2) W.G. was noted for his frequent wheezing. Eventually his mental state became so confused that the diagnosis of cerebral abscess secondary to bronchiectasis was considered. At post-mortem there were no obviously dilated bronchi and the brain appeared normal macroscopically. Old apical fibrosis indicated past pulmonary tuberculosis, but no recent or active lesion could be found, apart from bronchitis.

(3) W.C. appeared cyanosed, with clubbed fingers. He coughed less than many bronchitics and only wheezed during exacerbations of the disease. Investigation showed a red cell count of 7 million per c.mm., and a hæmoglobin of 118 per cent. His arm to tongue circulation time was 15 seconds, while his electrocardiogram showed right ventricular preponderance with some extra systoles. The sedimentation rate was only 5 mm., in an hour. The clinical features were bronchitis with a considerable amount of dyspnœa. He also had some osteoarthritis of the knees which needed treatment and limited his activity. There was a moderate degree of systolic hypertension, but less arterial thickening than the average.

The two most frequent complications of chronic bronchitis in aged subjects are bronchopneumonia and right ventricular failure. Yet it must not be forgotten that acute exacerbations of bronchitis, and even mere chronic bronchitis and emphysema alone, can be the causes of death. The work of Westlake (1954) is significant in this connection. He has shown that patients of the type under consideration suffer from respiratory insufficiency. They have impairment of gaseous interchange, leading to anoxæmia and acidæmia. Arterial oxygen arterial saturation is usually low and carbon dioxide tension is raised. These metabolic disorders are sufficient in themselves to produce a fatal outcome for some old people already staggering under a load of assorted pathology. When an element of infection is superadded to a pattern which includes some cardiac insufficiency, the respiratory compensation tends to break down. These facts have an important bearing upon the treatment of bronchitis in the aged.

Another clinical feature of the disease in elderly patients is the occurrence of left ventricular failure as an episode. Most of the subjects already show a systolic hypertension. In a series of 98 Chelsea pensioners with respiratory infections, some 18 had attacks of pulmonary œdema. Among these were 8 men who also showed right heart failure at some time or other. The differential diagnosis in a dyspnœic wheezing aged person can be difficult. In my experience, the most reliable sign is a noise like the receding tide on a pebbly beach, heard at the lung bases.

It will be noted that one of the clinical cases quoted above developed mental confusion as a terminal event. Psychosis and bronchitis are found

together in the aged from time to time and these patients may be divided into several groups. One consists of wheezing delirious cases with an undiagnosed underlying pneumonia. Another is the occurrence of senile dementia in an old person already subject to bronchitis. The third seems to be associated with the cerebral reactions to anoxæmia, acidosis and impaired gaseous exchange.

There is one type of chronic bronchitis found in those over 80 which has no counterpart in younger patients. It is commoner in females than in males. The complaint of cough is associated with wheezing and dyspnœa only on exertion. On examination the chest is small and moves poorly at the bases. Adventitious sounds are present chiefly in the lower part of the lungs. X-ray shows small lungs, increased bronchial markings, poor basal translucency and some enlargement of the left ventricle. Signs of vascular calcification may be seen, especially in the aorta. At autopsy there are signs of bronchitis combined with pulmonary congestion in lungs having atrophic emphysema. Calcification of laryngeal cartilages, bronchi and rib cartilages is usually present. The disease appears to be mainly degenerative in nature and ultimately associated with myocardial failure.

## Treatment

When treating bronchitis in aged patients, there are three important points to bear in mind. First: the seat of the disease is in the bronchi, rather than the alveoli of the lungs. Secondly, the triad of infection, bronchial spasm and cough are all harmful to a patient with some degree of cardiovascular degeneration. Thirdly, exudate, collapse and emphysema all render respiratory gaseous exchange ineffective. Some of these matters were discussed in an editorial annotation of the *British Medical Journal* (1954). It recommended the use of penicillin and streptomycin as antibiotics, advised the cautious use of oxygen to relieve anoxia, mentioned the use of broncho-dilators to relax spasms and condemned the employment of opiates.

In my experience, the use of oral and parenteral antibiotics has proved disappointing in the elderly while the disease has been bronchitis, but have been much more useful once consolidation has appeared. An explanation for this may be found in anatomy, for the blood supply of the bronchi is via the bronchial arteries, which are small branches of the aorta. A high concentration of antibiotics in the pulmonary circuit probably has little effect upon a chronic bronchial ulcer, since there is little anastomosis between the greater and lesser circulations.

It has been my practice, therefore, to treat bronchitis with aerosols, thus attempting to bring a concentration of antibiotics directly upon the seat of the disease. The results have been encouraging; my hospital wards, formerly containing many elderly bronchitic patients, now have a much lower number. Known cases of the disease attend for out-patient treatment at intervals during the winter and this often appears to prevent exacerbations of their bronchitis. The drugs usually employed are penicillin and streptomycin. They are dissolved in saline or a solution of 10 per cent. calcium chloride, which appears to diminish the viscosity of sputum. Since a Collison type of inhaler is used, anti-spasmodics such as aminophyllin can either precede, or be combined with, the antibiotic aerosol which is vaporised by oxygen, or oxygen and carbon dioxide (5%).

The number of inhalations administered varies from two to five a day. The present tendency is to increase the dose of antibiotic and to lessen the number of treatments. It is found that the flora of the sputum is changed towards the end of a week, so that only insensitive organisms remain. The amount of sputum is lessened within a few days. Periodic short courses of aerosols lasting five to seven days seem preferable to longer periods of administration. There is, otherwise, a real danger of a fungus infection in the lung which may be fatal. In these cases, the use of Nystatin has proved helpful (Stewart, 1956).

### Prognosis

As we have already said, chronic bronchitis is now one of the great killing diseases. The duration of the condition varies greatly. One patient under my care, now aged 97, states that her chronic cough began at the age of 30. Another man of 86 had no chest symptoms until seven years ago. Factors associated with a poor outlook are recurrent broncho-pneumonia, heart failure and the onset of mental confusion.

In assessing prognosis, however, it must be remembered that the bronchitis of the aged may only be one disease out of several from which they suffer. Such patients often die from cancer, gastric ulcers, cirrhosis of the liver, coronary occlusion and so on, with their pulmonary pathology only an incident in the final account.


## Summary

An account is given of chronic bronchitis as seen in elderly patients. Clinical and pathological findings are discussed. The value of aerosol therapy to aged bronchitic subjects is mentioned.


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# LUNG SCAR CANCERS

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The rising incidence of lung cancer during the past two decades has stimulated a search for ætiological factors, which has led to the incrimination of, among other things, heavy cigarette smoking and probably atmospheric pollution. Histological studies have also been directed to determining the site of origin and later spread of lung cancer. The importance of chronic damage to tissues as a predisposing cause of cancer development has been recognised for most sites and is an important factor in the genesis of a proportion of lung cancers.

Whilst studying the early stages in the development of lung cancer Raeburn and Spencer (1953) found that it was possible to relate many peripheral lung cancers to previous scarring, and it was also shown that all stages from simple reparative hyperplasia of bronchiolar epithelium to fully developed carcinoma could be found in association with lung scars. The observation has received further confirmation from the work of Rössle (1943) and Lüders and Themel (1954), and attention has now been directed to determining the causes of the lung damage which may result in neoplastic changes. The majority of lung cancers that have been clinically diagnosed are too large to furnish accurate information concerning their origin by the time the lung is removed at post-mortem or operation. Almost all the material illustrating the importance of scarring as an ætiological factor has been discovered by routine sectioning of all scars and suspicious areas in lungs examined post-mortem, supplemented by surgical specimens removed early in the course of the disease.

## Material

Twelve examples of small lung cancers growing in relation to scars of different ætiology have been selected from a larger collection of these lesions, and three examples of carcinomata arising from the walls of both a tuberculous cavity and chronic lung abscesses have been included.

*Case* 1. A man aged 58 was found to have a rounded radio-opaque mass in the upper lobe of the left lung. The left lung was removed at operation on the assumption that the nodule was a small cancer. Subsequent examination showed that the radio-opaque nodule was a small hamartoma, and in addition a small fibrocaseous tuberculous mass 1 cm. in diameter was found beneath the pleural surface of the upper lobe (Fig. 1). This was surrounded by an indefinite zone of pale grey translucent tissue 1-2 mm. in thickness. Microscopical exami-

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nation showed a fibrocaseous tuberculoma surrounded by a mantle of polygonal-celled carcinoma, the cells of which merged inperceptibly with simple non-neoplastic epithelium lining the fibrosed alveolar walls (Fig. 2). The regional lymph glands in the hilum of the upper lobe contained microscopical deposits of growth.

*Case* 2. A woman aged 68 died of bronchopneumonia. In the subapical region of the upper lobe of the left lung there was an area of caseation and fibrosis 3 cm. in diameter. Obvious secondary growth was found in the broncho-pulmonary lymph glands and one small secondary nodule in the brain. Microscopy showed an oat and polygonal celled carcinoma encircling and penetrating a fibrous scar containing caseous material and granulomatous tubercles. The regional lymph glands were partly filled with metastatic growth.

*Case* 3. A man aged 62 died from purulent bronchitis. Three months previously a secondary carcinoma, considered clinically to be a primary glioma, had been removed from the brain. In the apex of the upper lobe of the right lung was a nodule 2 cm. in diameter, composed of calcareous scar surrounded by greyish-white softer tissue. Growth was found in the hilar glands of the lobe and the right superior tracheo-bronchial and deep cervical glands. Growth was also present in the liver. Microscopical examination showed a polygonal celled carcinoma surrounding and growing out from the edge of obsolete fibrosed and largely calcified tuberculous nodules.

*Case* 4. A man aged 51 died from generalised purulent bronchitis. The apex of the right lung was densely adherent to the necks of the upper two ribs, sides of the first and second thoracic vertebræ and the dome of the pleura. Within the apical part of the lung was a greyish-white mass of tumour tissue 2 cm. in diameter with considerable fibrosis in the surrounding lung. Microscopical examination showed a polygonal celled, mucus-secreting carcinoma arising in fibrosed lung which also contained active granulomatous and healed tubercles.

*Case* 5. A woman aged 78 who died of heart failure due to essential hypertension showed a depressed scar beneath the pleural surface of the posterior and inferior part of the upper lobe of the left lung. On section there was a central anthracotic scar surrounded by greyish-white tissue with ill-defined edges. The whole measured 2 cm. in diameter. The regional glands were normal. Microscopical examination showed a small columnar-celled, mucus-secreting cancer growing on alveolar walls which was continuous with recognisable bronchioles lined by ciliated epithelium that had grown into a small central scar (malignant pulmonary adenomatosis) (Figs. 3 and 4). Outside the lesion there was a large branch of a pulmonary artery blocked by well-organised thrombus. The scar was probably due to a healed pulmonary infarct.

*Case* 6. A man aged 73 who died from bronchopneumonia showed in addition in the subapical part of the upper lobe of the right lung a scar beneath the pleural surface with a surrounding mantle of soft greyish-white tissue, the whole 2.5 cm. in diameter. Microscopical examination showed a poorly differentiated adenocarcinoma surrounding and penetrating the clefts in a dense scar. There were a few small areas of necrotic tissue but no evidence of a tuberculous lesion. Several small branches of the pulmonary artery at the edge of the scar were occluded by old, well-organised thrombus and there were areas

of epithelial hyperplasia in a neighbouring small bronchus. Although the cause of the scar cannot be stated definitely it appeared probable that it resulted from a healed infarct.

*Case* 7. A man aged 72 died of bronchopneumonia and a dissecting aneurysm of the aorta. The upper surface of the middle lobe of the right lung was puckered and scarred and on section there was an area of fibrosis surrounded by greyish tissue infiltrating irregularly into the surrounding lung. The whole measured 3 by 2 cm. A main lobar branch of the pulmonary artery was occluded by organised thrombus. Secondary carcinoma was found in the broncho-pulmonary glands, liver, adrenals and pancreas. The primary lung growth showed a mucus-secreting adenocarcinoma growing into and around an old scar. The latter contained necrotic areas with cholesterol crystal clefts and was traversed by a shrunken and tortuous branch of a pulmonary artery completely occluded by old organised thrombus.

*Case* 8. A case which had been reported elsewhere of a man aged 76 who died of confluent bronchopneumonia. Post-mortem examination showed a pleural scar 3 cm. in diameter on the surface of the lower lobe of the right lung, which extended 0.6 cm. into the lung beneath the scar. Microscopical examination of the scar showed severe chronic interstitial fibrosis resultant upon either collapse or infection with epithelialisation of the damaged lung. In places this epithelium had proliferated and heaped up and filled the alveolar spaces, whilst in other areas there were isolated solid nodules of carcinomatous cells (Fig. 5). No evidence of metastases was discovered and only the chance removal of the scar revealed the changes discussed above.

*Case* 9. A woman aged 74 died from a right intracerebral hæmorrhage and bronchopneumonia caused by essential hypertension. Terminally she had also had an acute bacterial endocarditis of the mitral valve which had caused several embolic infarcts in kidneys and spleen. In addition, on the back of the pleural surface of the upper lobe of the right lung there was a shrunken depression. On section this showed an old anthracotic scar surrounded by a mantle of greyish-white growth, the whole being 1.5 cm. in diameter. Secondary growth was found in the perivascular lymphatics draining the primary tumour and also in the broncho-pulmonary glands. One metastatic nodule was found in the liver. Microscopical examination showed a mucus-secreting adenocarcinoma arising around the sub-pleural scar and infiltrating the adjacent lung in a centrifugal fashion. The presence of growth in the perivascular lymphatic channels and regional glands was confirmed and growth was infiltrating the submucous lymphatics within the main bronchus.

*Case* 10. A man aged 59 died from purulent bronchitis and emphysema. In the upper and posterior paravertebral part of the upper lobe of the left lung a greyish-white mass containing some scar tissue 1.2 cm. in diameter was found a short distance beneath the pleural surface. A solitary metastasis was found in the left fifth rib. Microscopical examination showed a partly tubular, partly squamous-celled carcinoma arising in relation to the edges of a small scar of unknown ætiology (Fig. 6).

*Case* 11. A man aged 50 had complained of pain in the left side of his chest for three years, particularly if he bent down. During childhood he had repeated attacks of " bronchitis " which had persisted into adult life, and two

years before admission to hospital his chest had been radiographed and reported as normal. On admission he was breathless on exertion, clinical examination of his chest showed no abnormality, but a radiograph showed a uniform shadow in the subapical segment of the lower lobe of the right lung. A pneumonectomy was done and the growth, 3 cm. in diameter, was found (Fig. 7). The centre of the growth was occupied by a dark anthracotic scar mass 1.5 cm. in diameter surrounded by a lighter greyish-white tissue. Microscopical examination showed a poorly differentiated polygonal celled carcinoma growing out from a central scar that was continuous with a pleural scar. In the scar was a small artery occluded by organised thrombus. No growth was found in the broncho-pulmonary lymph glands.

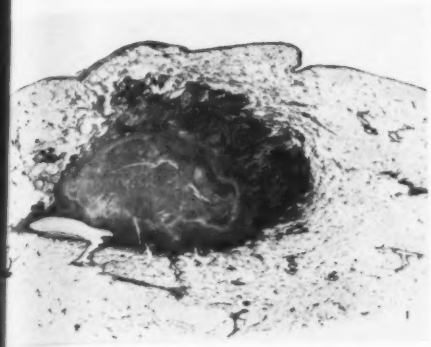
*Case* 12. A man aged 71 was admitted to hospital with a recent exacerbation of chronic bronchitis and progressive jaundice. A radiograph of the chest showed a bullet embedded in the lower lobe of the left lung. On further questioning the patient recalled that he had sustained a bullet wound in the chest forty years previously, and a faint stellate scar could still be seen in the fourth left intercostal space in the mid-axillary line. The patient died shortly after admission to hospital.

Post-mortem examination showed a generalised mucopurulent tracheobronchitis and bronchopneumonic consolidation in the lower lobe of the right lung. The lower part of the left pleural cavity was obliterated by dense adhesions and the lower lobe of the left lung was completely collapsed, fibrotic and bronchiectatic and showed a carcinoma arising in the posterior basal segment with lymphatic permeation extending to the broncho-pulmonary glands. Growth had spread from these glands into the wall of the lobar bronchus. The base of the bullet was touching the growth, the body of the bullet was enclosed in putty-like material, and the tip was embedded in the tenth rib (Fig. 8). The liver was largely replaced by secondary carcinoma and growth was present in the portal glands and tail of the pancreas.

Microscopical examination of the scar around the bullet showed a dense mass of hyaline fibrous tissue with calcareous and anthracotic deposits and cholesterol crystal clefts. Around part of the scar there was an oat celled and partly tubular, columnar and polygonal celled carcinoma with foci of squamous cells. Careful examination of the segmental and lobar bronchi showed bronchiectatic changes and permeation of the peribronchial lymphatics with growth. The mucosal surfaces of these bronchi were intact and the lining epithelium was clearly not the site of the primary growth.

*Case* 13. A woman aged 68 died from pulmonary tuberculosis. In the upper lobe of the right lung was a tuberculous cavity 7 cm. in diameter partly lined by a thick, grey friable membrane. There were calcified foci in the hilar glands. Microscopical examination of the inner wall of the cavity showed a well-differentiated squamous-celled carcinoma arising from metaplastic squamous epithelium lining the inner wall of the cavity.

*Case* 14. A man aged 60 was gassed during the first World War and subsequently suffered from winter coughs. Two months before admission to hospital he became listless and tired and his cough had become more persistent. At this time he developed a febrile illness diagnosed as " flu "; this improved after rest in bed for a week, but his cough remained unchanged. A radiograph of the chest showed an opacity with central cavitation in the anterior segment of the upper lobe of the left lung. A left upper lobectomy was carried out and



. 1.—(Case 1.) The sub-pleural fibrocaseous erculoma surrounded in part by darker growth. (×3)

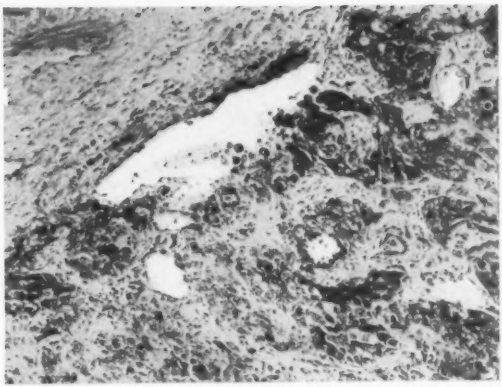
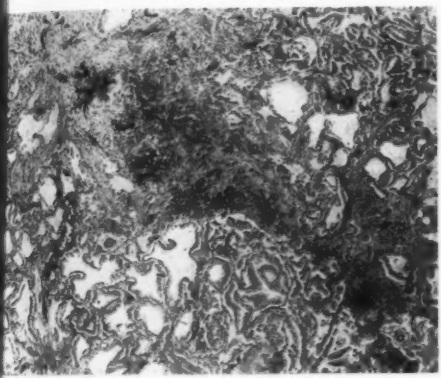


FIG. 2.—(Case 1.) High power view of growth shown in Fig. 1. The edge of the fibrous wall of the tuberculoma is seen in the upper left-hand corner. (×93⅓)



. 3.—(Case 5.) A tubular mucus-secreting cancer owing around the edge of an anthracotic scar. The oplastic tissue was continuous with recognisable bronchioles lined by ciliated epithelium. (×26⅔)

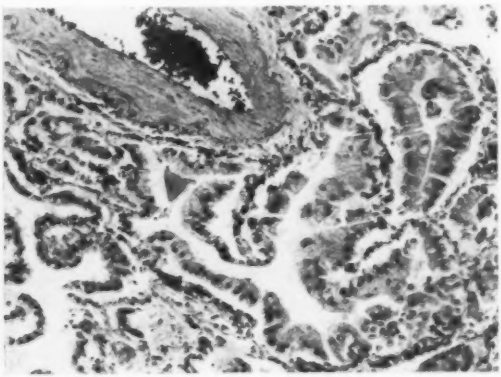


FIG. 4.—(Case 5.) The outer edge of the same growth as Fig. 3 where it has invaded normal lung. It shows the lepidic nature of the malignant cells which are lining undamaged alveolar walls using these as a framework. (×186⅔)

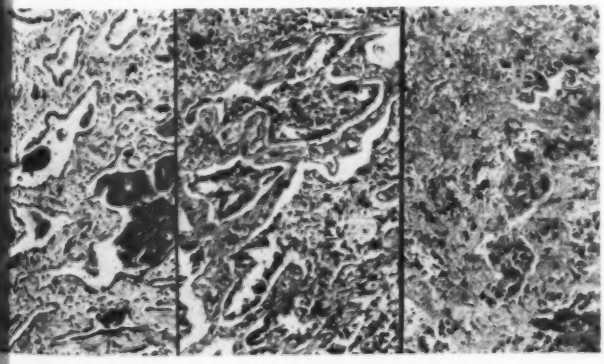


FIG. 5.—(Case 8.) A composite photomicrograph of closely related microscopical fields from the lung scar showing (A) A single layer of simple non-neoplastic epithelium lining damaged alveoli, (B) proliferation of epithelial cells shown in (A), and (C) small masses of carcinoma cells deeply embedded in anthracotic scar tissue. (×93⅓)

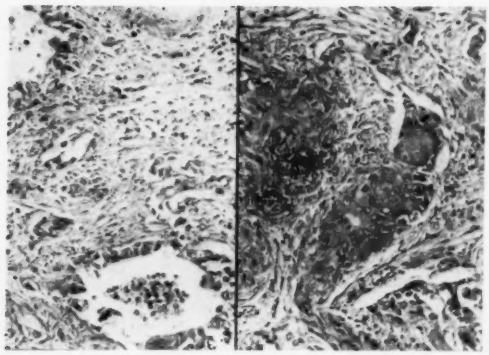


FIG. 6.—(Case 10.) Composite photomicrograph of adjacent low-power fields showing both tubular columnar celled and squamous celled growth arising in the same scar cancer. ($\times 93\frac{1}{3}$)

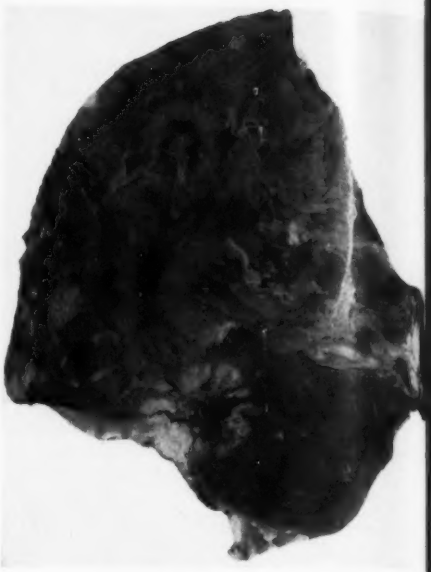


FIG. 7.—(Case 11.) Photograph of lobe of lung c taining a peripheral growth with a central d anthracotic scar surrounded by a mantle of ligh tumour tissue. ($\times \frac{1}{2}$)

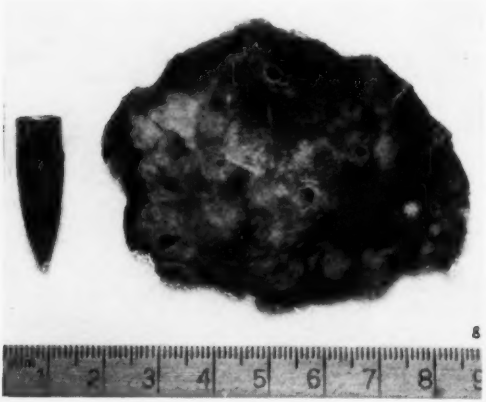



FIG. 8.—(Case 12.) Photograph of the growth surrounding bullet.

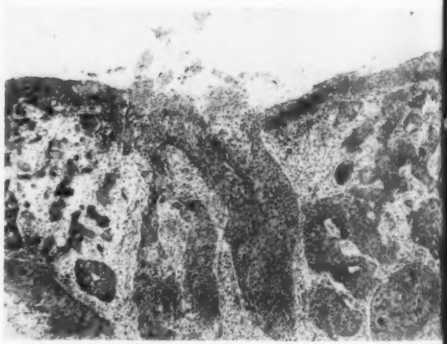


FIG.

FIG. 9.—(Case 14.) A low-pow section of the cavity situated n the pleural surface with grow arising in its wall and infiltrati adjacent lung. ($\times 1\frac{2}{3}$)

FIG. 10.—(Case 14.) Part of ca shown in Fig. 9 showing lin cells of metaplastic squam epithelium from which a squam celled cancer has developed a infiltrated the underlying ca wall. ($\times 26\frac{2}{3}$)

FIG. 9

some broncho-pulmonary glands removed. The upper lobe of the left lung showed depression of the pleura on the antero-lateral surface. On section a greyish-white tumour mass 4.5 cm. in diameter was found surrounding a cavity approximately 2.2 cm. in diameter situated beneath the pleural depression (Fig. 9). The nearest edge of the growth was 5.5 cm. from the hilum of the lung. The growth was sharply demarcated from the normal lung tissue and the surface of the cavity was lined by greyish-white tissue. Microscopical examination showed a chronic fibrous-walled cavity lined by squamous epithelium undergoing malignant change at many points (Fig. 10). The growth had spread into the adjacent lung tissue which showed well-marked bronchiectatic changes. It was not possible to state whether the cavity resulted from a chronic abscess or bronchiectasis, but the latter was present in the unaffected lung and was considered the more likely cause.

*Case* 15. A woman aged 64 had complained for three months of a productive cough and loss of weight. One month before admission to hospital she was treated at home for presumed right-sided pneumonia but failed to recover completely. On admission to hospital a radiograph of the chest showed collapse of the base of the right lung. Death eventually resulted from a massive embolus, and at post-mortem examination there was a cavity in the posterior and superior part of the lower lobe of the right lung approximately 2.5 cm. in diameter. Microscopical examination showed a thick fibrous-walled cavity continuous with a bronchus, lined by squamous epithelium which had undergone carcinomatous change and was spreading into the subjacent lung. The position of the cavity, its continuity with a bronchus, and the absence of tuberculous changes strongly suggested that it was a chronic abscess.

## Discussion

The importance of chronic inflammation as a factor in the causation of carcinoma in all organs is now well recognised and is an established fact. The lung is no exception and the cases cited above illustrate the general principle. The different behaviour of the large and the small bronchi to chronic inflammation makes it more convenient to discuss malignant change occurring in relation to the two sites separately.

Chronic inflammation in the large bronchi may lead to a varying degree of epithelial destruction, ulceration and eventually regeneration, but never leads to the formation of new bronchi in post-natal life, a feature which differentiates them from the small bronchioles situated in the periphery of the lung. The terminal bronchioles, however, are capable throughout life of considerable growth of new bronchioles, in the same manner as bile ducts proliferate in response to liver damage. This was first described by Friedländer (1876), again more recently by Montgomery (1944) in healing traumatic wounds in cats' lungs, and by Raeburn and Spencer (1953) in areas of scarring in human lungs. The borderline between innocent reparative hyperplasia and neoplastic change in many sites is often indistinct and the former process may occasionally merge imperceptibly into the latter. The factors influencing the development of malignant change in areas of chronic inflammation are unknown, but in many instances stromal changes, including scarring, may influence the epithelial tissue in time leading to malignant transformation. Also the type of scar tissue laid down may influence the subsequent develop-

ment of malignant change (Orr, 1938), and Gillman *et al.* (1955) have stated that elastotically degenerate collagen predisposes to the development of cancer in skin scars. In the lung, most peripheral scars consist not of pure collagen but almost entirely of fibres that stain positively with certain elastic tissue stains, notably Weigert's stain, and referred to as elastotic scar tissue.

Furthermore, following destruction of alveoli and respiratory bronchioles the subsequent scarring causes obstruction to the lymphatic drainage, following which anthracotic pigment and other particulate matter becomes localised and trapped within the scar. The possibility that adsorbed carcinogens may be concentrated and localised in this process merits further careful attention. Also, some of the scars and enclosed necrotic areas have contained cholesterol, which in view of the carcinogenic properties of this substance, shown by Hieger (1949), may be an exciting factor in producing carcinogenic changes.

The group of cancers arising in relation to peripherally situated lung scars will be described first.

Although only a minute proportion of all lung scars undergo malignant change it has been possible to demonstrate all degrees of intermediate change ranging from simple bronchiolar proliferation through atypical hyperplasia to malignant tumour formation (Raeburn and Spencer, 1953). Several reports of atypical bronchiolar hyperplastic changes in fibrosed lungs have now appeared (King, 1954; Spencer and Raeburn, 1954).

The ætiological factors concerned in the causation of lung scars are varied. In the present series Cases 1-4 and 13 appeared to be related to definite healing tuberculous lesions. Woodruff and Nahas (1951), Woodruff *et al.* (1952), and Hambly (1952) have described the association of lung cancer with chronic pulmonary tuberculosis. In some cases the growths arose in relation to the walls of old fibrocaseous tuberculous foci, as in cases 1-4 and as described by Woodruff *et al.* (1952). In many growths of this type the tumour is a well-differentiated adenocarcinoma arising from newly formed bronchioles growing in the edges of the scar tissue. In others the growth appears to have arisen from the epithelium lining damaged alveoli (case 1). The origin of the epithelial cells that line damaged alveoli is still uncertain, some maintaining that such alveolar epithelium results from down-growth of respiratory bronchiolar epithelium, whilst others maintain that it is derived from pre-existing normal alveolar epithelium stimulated by chronic inflammation.

Infarction appeared to be the most probable cause of the scarring found in cases 5, 6 and 7. In every case the presence of a large shrunken branch of a pulmonary artery filled with old organised thrombus, in some cases outside the confines of the lesion, lent support to this view (cases 5, 7). The probability that many of the scars resulted from healed infarcts is rendered likely, as we have found that about 40 per cent of lungs examined in hospital adult post-mortems contain small pulmonary emboli when carefully examined. Many of these emboli are small and only occur during the terminal illness, but a proportion of lung scars enclose necrotic tissue and often show organised intra-arterial thrombi and have in all probability resulted from a previous infarct.

One example of a bullet injury and subsequent scarring causing a carcinoma has been included, and similar cases have been reported by Bergeret, Hirschberg and Millot (1931), Luckow (1933), Huguenin, Fauret and Bourdin (1947),

König (1952) and Siddons and MacArthur (1952). Inhaled metallic foreign bodies have also been reported as giving rise subsequently to malignant change, and these have included a scarf pin (Weiss and Krusen, 1922) and a crucifix (Blake, 1943). In all cases the latent interval between wounding or inhalation of the foreign metallic body and the appearance of the growth has been very long, amounting to a half or more of the individual's life span. Experimental cancer research has shown repeatedly that the interval between the application of a carcinogen and the development of the resulting tumour often amounts to a third or more of the animal's life span. The possibility that the metal itself may also have behaved as a carcinogen in these cases has to be considered in addition to the changes stimulated by the scarring.

Certain forms of pneumoconiosis causing fibrosis have also been found to give rise to lung cancer, notably asbestosis (Kennaway and Kennaway, 1947; Gloyne, 1951; Bonser, Faulds and Stewart, 1955), and hæmatite miners' lung (Faulds and Stewart, 1956). Anderson and Dible (1938) considered silicosis also predisposed to carcinoma, but this has been refuted by Hadfield (1953).

Chronic infections and collapse are also responsible for producing lung scars, in addition to damage of the large bronchi, and they probably account for many of the peripheral lung scars of undetermined ætiology; case 8 was probably the result of such changes.

All histological varieties of lung cancer (including squamous, polygonal, oat and columnar celled adenocarcinomata) have been found originating around scars. The well-differentiated, often mucus secreting adenocarcinoma was the most commonly encountered type and the cells frequently exhibited well-marked lepidic characteristics once they had grown outwards away from the site of origin. This type of growth is often referred to as malignant pulmonary adenomatosis and metastasises early by the lymphatic vessels to the hilar glands. Although well-differentiated squamous-celled growths usually arise in the larger bronchi, an example of this type of growth was found mixed with an adenocarcinoma in case 10 and has been reported previously. A similar peripherally situated squamous celled scar cancer was reported by James and Pagel (1944).

The wide variety of ætiological factors that may be responsible for producing scarring and damage to the lung shows that it is the damage to the lung rather than the factor responsible for the damage that either initiates malignant change in lung scars or renders the epithelium in the scarred area susceptible to environmental or internal carcinogens.

The importance of lung scars in the genesis of peripheral lung cancer has been proved histologically, but the authors have not attempted to determine what proportion of lung cancers start in this fashion, although Raeburn (1954) found that, in a series of forty-one circumscribed peripheral carcinomas twenty-five (60 per cent.) contained scars. Walter and Pryce (1955) have shown that approximately 50 per cent. of cases in which the site of the primary growth could be determined accurately occurred in the periphery of the lung. Of these 55 per cent. showed central scars. This figure is in close agreement with the findings of Lüders and Themel (1954), who have stated that 28·4 per cent. of all lung cancers arise in scars. From these figures it would appear that at least a quarter of all lung cancers today are related to lung scars.

It is certain that many growths considered clinically to have arisen in the large central bronchi are in fact secondary growths, as was suggested by us previously (Raeburn and Spencer, 1953). The rapid centripetal lymphatic spread of peripherally arising cancers leads to metastatic growth in the hilar glands of the lung before the patient complains of symptoms and seeks treatment. From these glands retrograde lymphatic spread into walls of adjacent lobar bronchi not infrequently simulates a primary growth arising in these structures. This suggestion has received confirmation from radiological follow-up of early cases of peripheral lung cancer by Rigler, O'Laughlin and Tucker (1953).

The other group of cases (cases 13, 14, 15) arose from metaplastic squamous epithelium lining a chronic abscess, bronchiectatic or tuberculous cavities. In all these conditions the cavities are derived from or are in continuity with large or medium-sized bronchi. In each case the cavity may ultimately become lined by metaplastic bronchial epithelium. In all three instances chronic inflammation led to damage and squamous metaplasia of the bronchial epithelium, which in case 13 grew into the tuberculous cavity in an attempt to epithelialise its surface. The importance of chronic bronchiectasis as a predisposing factor in the origin of carcinoma has been described by Tuttle and Womack (1934), who claimed that one in every seven patients with primary bronchiectasis, living until the usual cancer age had been reached, developed lung cancer. Bryson and Spencer (1951) found four examples of similar growths in their large series of lung cancers. Woodruff and Nahas have also described similar growths arising in a chronic tuberculous cavity, and Faulds and Stewart (1956) an example of carcinoma arising in the wall of a chronic abscess.

These well-differentiated squamous-celled cancers are quite distinct from the atypical bronchiolar proliferations, an example of which was described by Stewart and Allison (1943) and which may occasionally become malignant as described by Cureton and Hill (1955). This group of atypical bronchiolar proliferations is closely related to the peripheral scar cancers and arises in the fibrosed lung from small bronchioles.

In addition to the proved histological relationship between chronic lung damage and lung cancer, statistical clinical evidence of the relationship of chronic antecedent pulmonary infection to lung cancer has been furnished by Bryson and Spencer (1951), Doll and Hill (1952), Anon. (1954), Case and Lea (1955) and Fincke (1956). The conclusion therefore seems clear, both from the pathological and clinical evidence, that chronic inflammation of the lung leading to structural damage is an important factor in causing lung cancer, particularly those growths arising in the periphery of the lung.

## Summary

Twelve scar cancers and three cases of cancer arising in chronic lung cavities have been described. The importance of chronic inflammation as an exciting factor in lung cancer has been described, particularly with reference to the peripherally situated growths. The ability of the terminal bronchioles to proliferate all through life in response to lung damage differentiates these structures from the large bronchi. Reparative hyperplasia of small bronchioles may

progress to malignant change and all histological types of lung cancer can result, though columnar-celled tubular cancers are the commonest. The causes of the lung damage included chronic infection, tuberculosis, infarction and foreign bodies. Damage and scarring of the lung was the essential factor and the cause of such change was of secondary importance. The early spread of cancer from small peripheral growths to the regional lymph glands and lobar bronchi was demonstrated, and the possibility of such secondary spread to lobar bronchi being confused with a primary growth arising in these structures is emphasised.

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# THE PANCOAST SYNDROME

By N. S. Dontas

From The London Chest Hospital

Primary carcinoma of the lung producing the Pancoast syndrome has hitherto been regarded as inoperable, based on the assumption of clinical and radiological evidence. Nevertheless, surgical treatment has been carried out with encouraging results.

The syndrome is produced by a growth of the thoracic inlet which causes neurological disturbances from pressure on the upper thoracic nerves, as well as a Claude Bernard-Horner syndrome. It was first described by Pancoast as " an apical chest tumour." In 1932 he had reviewed 7 cases and called them "superior pulmonary sulcus tumours." Pancoast's original description gave a hopeless prognosis and indicated that neither surgery nor irradiation was of any value as palliative treatment.

In 1946 Herbut and Watson reported 151 cases producing the Pancoast syndrome: they described these as tumours of the thoracic inlet. Among these, 100 were primary carcinomata of the lung and the rest were due either to a primary growth of the neck or of the thyroid gland. They found that a few were caused by secondary metastases growing in the thoracic inlet.

Very few thoracotomies have been performed for the removal of a primary carcinoma of the lung producing the Pancoast syndrome and in none of these could the growth be removed. In 1950 Chardac and MacCallum described a case where the tumour was removed by lobectomy. The patient had a course of radiotherapy to complete his treatment and survived for nearly six years. He died from broncho-pneumonia and no evidence of metastases could be found at the post-mortem examination. Notwithstanding that the main cause of the Pancoast syndrome is a malignant growth, cases have been reported where a benign tumour has had the same effect.

In 1950 Ashe *et al.* had 1 case in which a non-specific pneumonitis of the left upper lobe produced a Pancoast syndrome. In 1954 d'Eshougues and Honel described the same syndrome caused by hydatic cyst of the spine: this was cured by removal of the cyst. Recently, in 1956, Hirtenstein described 1 case producing the same syndrome through acute osteomyelitis with erosion of the right transverse process of the first dorsal vertebræ; symptoms subsided after treatment with chemotherapy.

Although quite frequently chronic pulmonary tuberculosis produces a collapsed upper lobe and a contracted thoracic inlet, no association between Pancoast's syndrome and tuberculosis has been found. Only 1 case has been described where the syndrome was caused by tuberculoma.

Since 1953 4 patients have been admitted to the London Chest Hospital suffering from primary carcinoma of the lung complicated by the Pancoast

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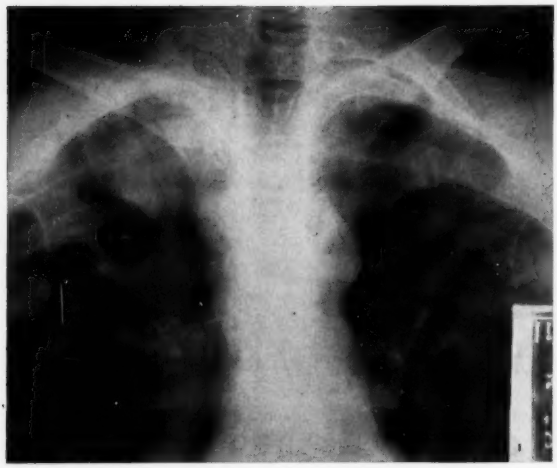

FIG. 1.—Case No. 1. Growth at the right apex, erosion of the 2nd rib is obvious.

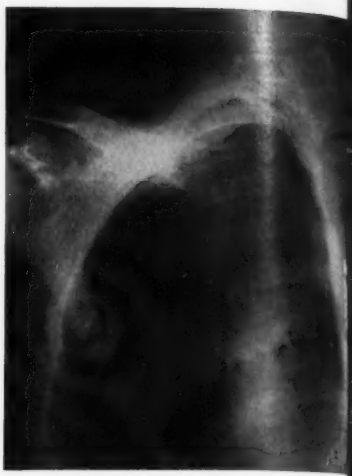

FIG. 2.—Case No. 2. Very small peripher carcinoma at the right apex. On pla X-ray, erosion of the 3rd rib is not obvio

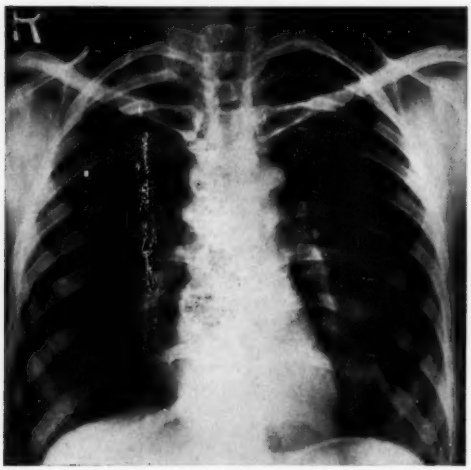

FIG. 3

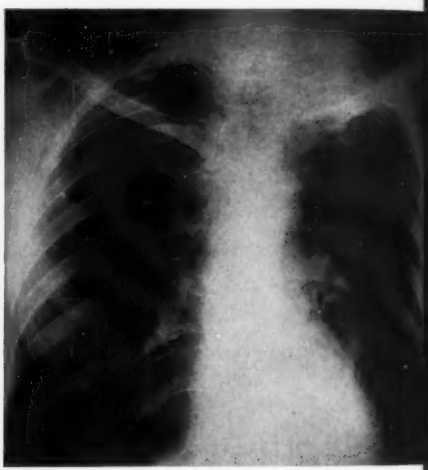

FIG.

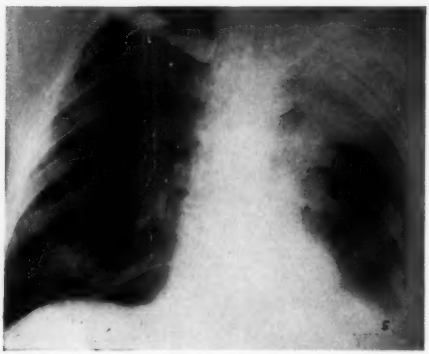

FIG. 5

FIG. 3.—Case No. 3. Carcinoma at the right apex w erosion of the 1st rib.

FIG. 4.—Case No. 4. Carcinoma at the apex of the lung, which was fixed to the three upper vertebr

FIG. 5.—Case No. 4. Post-operative X-ray. The th upper ribs were resected and a polythene pack was in the chest.

*To face p.* 247

syndrome. All these patients have been treated surgically and their history is as follows.

*Case No.* 1. In July 1953 a man, aged 53, started complaining of severe pain over the back of the right shoulder radiating down the medial border of the right arm. Slight cough with little sputum had become more persistent during the previous few months. He was admitted to hospital in January 1954 and on examination a right Horner's syndrome was present. The right arm was warmer than the left and loss of power was noted in the right hand. X-ray showed a shadow in the right apex with erosion of the neck of the second rib (Fig. 1). On 20.1.54 a thoracotomy was performed and a small growth confined to the apical segment of the right upper lobe was present. The lung was separated from the chest wall. In view of the great enlargement of the hilar glands, no resection was undertaken but a biopsy was taken. The histological report proved it to be a primary squamous carcinoma of the lung. Post-operatively the pain in the arm disappeared completely.

*Comment:* The thoracotomy and the mobilisation of the lung greatly relieved his pain from the root of the nerves, and although his condition deteriorated and he died in August 1954, the operation was thoroughly justified.

*Case No.* 2. A man aged 70 complained of a winter cough for the last twenty years. In August 1952 he had an acute illness and since then has had increasing general lassitude. In April 1953 he noticed pain in the right shoulder radiating to the front of his chest and to the inner surface of the right arm. He was admitted in October 1953; radiological examination showed an opacity at the right apex and tomograms showed erosion of the third rib (Fig. 2). He had a wasting of the right thenar eminence and a slight Claude Bernard-Horner syndrome was present. His sputum was negative for A.F.B. and malignant cells and bronchoscopy was normal. On 16.11.53 a thoracotomy was undertaken. There was an apical peripheral carcinoma of the lung which was invading the posterior ends of first, second and third ribs. An upper lobectomy was performed and the posterior ends of the affected ribs were resected. Histology of the specimen showed a peripheral adenocarcinoma with an invasion of second and third ribs by neoplasm.

*Comment:* He died in October 1956 from generalised carcinomatosis. During the three years after his operation the pain in his arm no longer existed.

*Case No.* 3. In January 1955 a woman aged 31 noticed a tenderness round the shoulder and the scapula which was radiating to the right elbow and ulnar aspect of the forearm. She had a little cough and a small amount of purulent sputum. She was admitted in April 1955, when her general condition was poor. On examination she had slight diminution of pin-prick sensation over the distribution of T.1 and T.2. There was a partial Horner's syndrome on the right side (X-ray see Fig. 3). On 28.10.55 a right thoracotomy disclosed a very small hard growth in the apical segment of the right upper lobe with obvious involvement of T.1 and T.2. The glands in the superior mediastinum were enormously enlarged and especially a chain under the azygos vein. In view of her age and the local condition it was decided to carry out palliative treatment to relieve this pain. A wedge resection of the apex of the lung was performed to prevent further local pressure and small portions of nerves from T.1 and T.2 were removed. Post-operatively the pain was very much better and she was discharged to complete the treatment with a course of deep X-rays.

*Comment:* The patient had incomplete radiotherapy owing to deterioration of her general condition. The histology of the resected specimen proved to be an undifferentiated carcinoma invading the portions of the nerves which were resected. Five months later she developed a large mass in the neck eroding the first and second thoracic vertebræ, but she did not complain of any pain. Whether it was a further extension of the primary tumour or secondaries in the spine could not be established with certainty. She died of generalised carcinomatosis in February 1956.

*Case No.* 4. In August 1954 a man aged 50 started complaining of pricking pains at the lower end of the left scapula; these started radiating to the anterior aspect of the left chest and the under-surface of the left arm a few weeks later. In April 1955 he was admitted and X-ray showed a shadow in the left upper zone; there was no rib erosion (Fig. 4). On examination wasting of the muscles of the hand was noted. A left Horner's syndrome was present and a difference in blood pressure in the left arm, 150/90, by comparison with the right arm, 135/90, was observed. On 2.5.55 a thoracotomy was undertaken. A hard mass was found in the apex of the upper lobe; this was fixed to the mediastinum and necks of the upper three ribs and to the sides of the vertebræ. The transverse processes of the upper three vertebræ were divided and the growth was seen to involve the first thoracic nerve and the sympathetic chain. These were resected, leaving some growth over T.1. The left upper lobe was removed and no glandular involvement could be identified. At the end of the operation a large space was present under the scapula, and to prevent paradoxical movement a polythene pack was inserted (Fig. 5). Post-operative convalescence was uneventful and the patient was totally relieved from pain.

*Comment:* Histology proved the growth to be a primary undifferentiated carcinoma of the lung involving the pleura and the attached ribs. T.1 was invaded by growth as well as the fragment of the sympathetic nerve. Although he died in October 1956 it was thought that the operation was absolutely essential.

## Discussion

The above 4 cases of primary carcinoma of the lung producing the Pancoast syndrome were treated surgically. Operative treatment for this type of malignant growth must be carried out as a palliative measure. The main disability of the patient is severe and persistent pain over the T.1 and T.2 area, due either to pressure or infiltration by growth of these nerves.

Operative treatment can be effected by mobilisation of the apex of the lung which frees the growth and thereby reduces the pressure on the brachial plexus and the sympathetic trunk. The beneficial effect of this apicolysis was observed in case No. 1, where no resection was done. The persistent pain in the arm, due to the pressure on the plexus, disappeared completely. The same palliative treatment was undertaken in case No. 3. The grossly enlarged lymph nodes and the age of the patient convinced us that no radical surgical procedure could be performed. Wedge resection of the apex of the lung had a very good effect on the patient's symptoms. When the symptoms are due to the infiltration of the upper thoracic nerves, the resection of the affected nerves relieves the pain completely and does not produce any further disability in the patient.

A thoracotomy with a view to radical resection and treatment of a primary carcinoma of the lung that produces a Pancoast syndrome ought to be under-

taken. The surgical approach to the chest with a long incision as described by Chardac is essential, because of the necessity for the removal of the posterior ends of the first, second and third ribs. This happened in three of our cases which had presented with rib erosion.

The treatment of the thoracic nerves must be radical and removal of good lengths of T.1 and T.2 essential. The type of resection which is necessary for this type of tumour is always lobectomy. The neoplasm does not extend into the lung but invades the pleura. We have not, so far, found any explanation for the lack of extension of the growth at the expense of the lung. Of our cases two had successful lobectomies and one survived for three years, the other over a year.

Another important factor before the surgeon during the operation is the management of the roof of the thoracic wall, for the removal of the upper lobe with the attached portions of the ribs leaves a relatively large space which excludes an air-tight closure of the chest.

Paradoxical respiration is a usual and dangerous sequel. This, in case No. 4, was treated by an application of a large polythene pack which was left lying on the lung. A relatively small leak stopped forty-eight hours after the operation and no subcutaneous emphysema appeared.

One of the factors influencing the prognosis of a primary carcinoma of the lung is the lymphatic spread which produces generalised carcinomatosis. In this type of growth the spread is not only conducted through the lymphatic vessels of the upper lobe of the lung, but also, by invasion of the ribs, it follows the lymphatic drainage of the intercostal spaces. The intrathoracic lymph nodes usually involved are those of the superior mediastinum. The glands of the subcarinal area have so far been found, in our cases, to be free from metastases.

Another way of spread is the invasion at an early stage of the supraclavicular area. The infiltration can reach this area following the lymphatic vessels which are present in the adhesions attached to the apex of the lung.

There is no evidence that tumours producing the Pancoast syndrome are affected by one special type of cell. Among our cases two were found to be undifferentiated, one adenocarcinoma, and the last was due to a squamous cell carcinoma.

Radiotherapy has given a fair outlook to the arrest of the disease. Haas and others (1954) note a re-calcification of the rib which has been given local fibrosis and circulatory disturbances are produced. The combination of surgical treatment with radiotherapy would give the best hope in the management for this type of growth.

## Summary

Four cases of primary carcinoma of the lung producing the Pancoast syndrome are described.

All these cases were treated surgically by thoracotomy and in three of them the tumour was removed. Palliative treatment has been effective by mobilisation of the apex of the lung. The combination of surgery and radiotherapy should be considered as necessary for the treatment of this type of growth.

## Addendum

Since the preparation of this paper 4 more cases of primary carcinoma of the lung producing the Pancoast syndrome have been treated surgically by removal of the upper lobe and part of the attached ribs. All 4 cases had a course of post-operative radiotherapy.

I wish to express my thanks to Mr. J. R. Belcher, for his advice and help in the preparation of this paper, and also for permission to publish his cases.

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# COUGH FRACTURE OF THE RIBS

By J. E. G. Pearson

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Fracture of a rib due to coughing must be the commonest form of stress fracture, though other violent contractions as in sneezing or vomiting can also produce it. Savage (1956) attributed the first description of a cough fracture to Graves in 1833, and he found 144 cases reported in the literature of which the great majority had been in patients suffering from pulmonary tuberculosis (Oechsli, 1936; Richardson, 1936; Sakka, 1938; Cohen, 1949). He added 3 cases to the 13 already described as occurring in pregnancy—perhaps a surprisingly small number for a fairly well recognised association.

In the non-tuberculous sphere, Harvey (1944) found 18 cases of rib fracture in a review of 500 patients suffering from atypical pneumonia; these occurred during one winter in an American Army station hospital, presumably all in males, although this point is not specifically recorded. Mitchell (1951) also studied the incidence in 720 chest clinic attendances and found 14 cases of cough fracture.

The present series has been collected over a six-year period (1951-56 inclusive). The total number of new patients seen approximated 4,500 and the number of patients considered to be affected by cough fractures of the ribs numbered 28; it should be emphasised, however, that the rib fracture was in a few of these not the initial symptom but occurred while the patient remained under observation.

In no case was active pulmonary tuberculosis or pregnancy present at the time of the fracture; nor did the patients show any evidence at the time or at later follow-up of any decalcifying process or other local pathological state which might have predisposed to it, except one female, age 45, in whom slight osteoporosis was suspected, but in whom all investigations including blood calcium, phosphorus and alkaline phosphates were normal.

The following table shows the salient features of the 28 cases of cough fracture:

*Males* 9; *Females* 19. Total 28.

*Age Distribution:*

| 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71-80 |
|---|---|---|---|---|---|
| 2 | 5 | 7 | 9 | 4 | 1 |

*Side: Right* 6; *Left* 13; *Both* 9.

(*Received for publication March* 2, 1957.)

*Number of times ribs involved:*

| | *Right* | *Left* |
|---|---|---|
| Rib III .. .. | 2 | 0 |
| IV .. .. | 0 | 0 |
| V .. .. | 1 | 0 |
| VI .. .. | 7 | 6 |
| VII .. .. | 5 | 6 |
| VIII .. .. | 3 | 7 |
| IX .. .. | 3 | 6 |
| X .. .. | 4 | 7 |
| | 25 | 32 |
| | 57 | |

| | |
|---|---|
| Number diagnosed in the acute stage .. .. .. .. | 16 |
| Number diagnosed only at stage of X-ray callus formation .. | 6 |
| Number diagnosed with old fracture and suggestive history before coming under observation .. .. .. .. .. | 6 |

*Morbid conditions associated:*

| | |
|---|---|
| *Asthma, emphysema, bronchitis, bronchiectasis .. .. | 20 |
| Pneumoconiosis .. .. .. .. .. .. .. | 1 |
| Bronchopneumonia .. .. .. .. .. .. .. | 1 |
| Influenza .. .. .. .. .. .. .. .. | 1 |
| Bronchial carcinoma .. .. .. .. .. .. | 1 |
| Upper respiratory infections, presumed tracheitis .. .. | 4 |

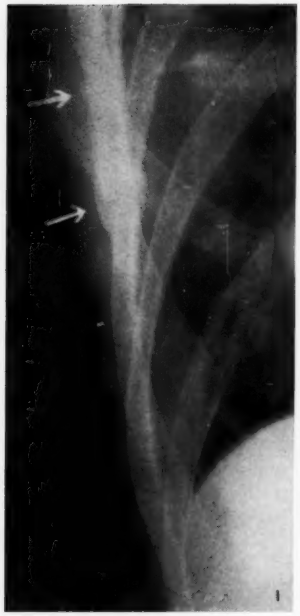
* In this group, one case followed lobectomy for bronchial carcinoma and one occurred after pleurodesis for spontaneous pneumothorax.

## Discussion

Even when pregnant and tuberculous cases are omitted, women seem to be affected twice as frequently as men by cough fracture; as in the present series, 10 of Mitchell's (1951) 14 patients were females, as were 6 out of the 9 seen by Wynne Williams (1951). The exception is the male series mentioned above by Harvey (1944). There is a wide range of age incidence from the third to the eighth decade with no evidently increased liability beyond the age of 60.

Fractures other than in sixth to tenth ribs on either side were very uncommon. In Wynne Williams' (1951) cases involvement was between sixth to eleventh ribs, which he described as "usual"; Mitchell (1951), however, found occasional involvement of second and fifth ribs as in the present series. The preponderance of left-sided fractures seems to be a nearly constant finding, but in "chest" cases it does not seem nearly so striking as those occurring in pregnancy (Savage 1956). Almost half the subjects (13 patients) broke more than one rib. The incidence of bilateral involvement in nearly one-third of the present cases seems higher than previously realised, but includes two patients who broke ribs on the opposite side some considerable time after the first fracture. In one of these, a woman aged 32, the sixth rib was involved alone on each side in mirror-image fashion at an interval of six months.

Even in tuberculous or pregnant patients it seems to be agreed that osteoporosis is not present as a predisposing factor. Paulley *et al.* (1949) found normal blood calcium and phosphorus levels in their 4 cases complicating



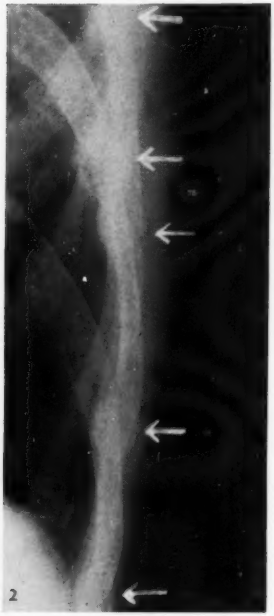
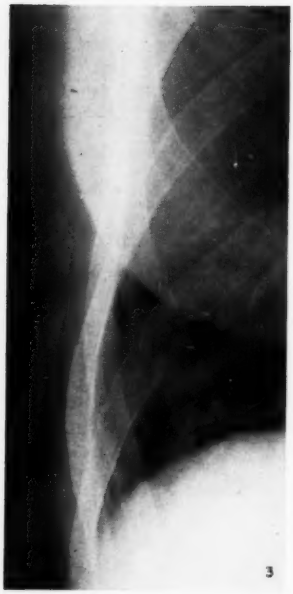
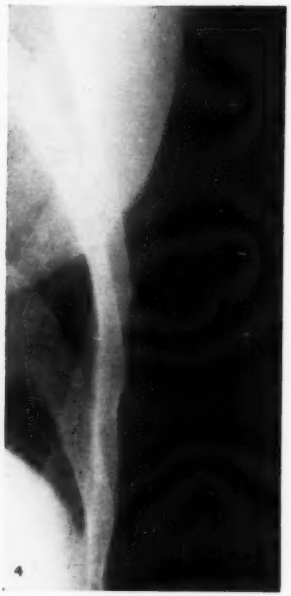


FIG. 1.—Rib fractures with callu
Right 6 and 7.

FIG. 2.—Left, 6, 7, 8, 9 and 1





FIGS. 3 and 4.—One year later
minimal residual change.

*To face p.* 253

cyesis, and pointed out that fractures do not occur in the puerperium when decalcification would be just as liable to be present.

The theory put forward by Oechsli (1936) to account for the main fracture sites also seems to have been accepted; his line corresponds to the interdigitation of the external oblique muscle of the abdomen inferiorly (ribs 6-12) with serratus anterior (ribs 1-8) and runs from a point on the fourth rib 4 cm. from the costochondral junction to the ninth rib in the midaxillary line. Savage (1956) adds the costal slips of latissimus dorsi (ribs 9-12) as relevant to the lower fractures.

In the present series all except four of the fractures occurred in the axillary region, but twenty-four of these were in the posterior axillary line, the same number in mid-axilla and only five in the anterior axilla. Those in the posterior axilla showed no preponderance in the lower ribs of those mainly involved (6-10) and it would seem that the previous mechanical theory of causation, while basically correct, has attempted too much precision about the sites of cough fractures: the present findings might suggest that of all the muscle stresses that produced by the obliquus externus abdominis is the most operative.

## Diagnosis

This depends largely on a careful history, eliciting the onset of chest pain during a coughing bout, possibly associated with the feeling of something snapping. This should lead to a search for any tender spot on a rib, followed by scrutiny of the chest radiogram, with special views of the axillary portions of the ribs as required. Naturally an awareness of the relative frequency of the condition may also be an aid to diagnosis. Pleural friction, if heard, is more likely to lead to an erroneous than a correct diagnosis; it was described by Swineford and McKinnon (1945) and was heard in 2 cases of the present series.

Several authors have emphasised how easily a cough fracture may be missed on casual inspection of a skiagram, the reason being possibly threefold: (1) the axillary position of most of the cracks; (2) minimal, if any, displacement at the fracture site; and (3) the obscuring of some of the lower ribs by the diaphragms and possibly breast shadows. Most easily overlooked will be those which have an atypical history with only gradual pain onset. Of the present series 6 were only diagnosed after callus had started to form. Complete healing of the fracture with absorption of the callus leaving a normal radiogram of the ribs is probably the usual outcome (Figs. 1, 2, 3, 4). There may, however, be sufficient residual displacement or angulation to mark the site of an old cough fracture, and it was thought that in this series a further six such abnormalities were found indicating the event long before the first skiagram.

Thus of the cases recorded only 22 can be said to have occurred during the actual period of observation of about 4,500 patients, so that the incidence of cough fracture in general thoracic work could not be placed higher than 0·5 per cent. in non-tuberculous subjects. This is considerably lower than Mitchell's (1951) figure of nearly 2 per cent. in 720 cases, but even so the condition would seem to be more frequent than is generally realised.

**Summary**

The main features are described of 28 cases who were considered to have sustained fifty-seven rib fractures due to cough of non-tuberculous origin.

Some assessment of the frequency of this condition to be expected in thoracic work is attempted, and some of the difficulties in diagnosis are emphasised.

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# STRESS FRACTURE OF THE FIRST RIB OCCURRING IN TWO SISTERS

By F. L. Kronenberger

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The occurrence of stress fracture became the subject of interest and discussion when, during the second World War, the radiological screening of large groups of the population revealed a considerable number of these fractures (Blair Hartley, 1943). Although march fracture affecting the lower limbs has been widely recognised since the end of the last century, particularly in the literature of the European Continent, very little was known of stress fracture of other bones. Alderson (1944) in a paper "Stress fractures of the first rib" described 35 cases of anomalies of one or both first ribs discovered in 55, 415 routine fluorographies of Royal Naval personnel which included 3,433 women. He found various forms of transverse or oblique breaks of the first rib, either partial or complete, associated with fusiform swelling around the lesion, due in some cases to callus formation. In other cases the lesion was of longer standing and the surrounding swelling had the appearance of fully formed bone. All the 35 cases were males. In a further paper Alderson (1947) analysed 73 cases of first rib fracture which he detected during the examination of 77,607 male naval personnel; some of the fractures in this group were, however, true fractures with a history of trauma. In the U.S.A. Bowie and Jacobson (1945) reported on 62,789 radiological examinations of the chest and collected 17 cases of anomalies of the first rib "which could be interpreted as being due to fracture." Nevertheless the American authors concluded that the callus and pseudarthrosis-like changes were due to anomalous development and did not represent any type of fracture. Powell (1950) described 25 cases of fracture of the first rib of the type we are here concerned with, and all with one exception, were diagnosed in army servicemen.

## Case Reports

During the routine examination of "contacts" at the chest clinic the radiographs of two sisters showed fractures of the first rib. Both sisters were employed at an egg packing station, where three to four times weekly two out of seven female employees lifted boxes weighing 60 to 70 lb. to a wagon at a height of 50 inches. They usually lifted eighty boxes a day. The sisters were healthy-looking, plump girls of average size without physical abnormality or history of trauma.

*Case* 1. Sister A., aged 18 years, had been working at the station for three years when a radiograph in June 1954 showed an oblique fracture of the first right rib without obvious callus formation, and at the first left rib a transverse irregular fracture surrounded by callus in fusiform formation (Fig. 1). Two

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months later the girl left the station and in January 1955 a film demonstrated callus around the break of the first right rib and signs of some more healing of the fracture of the left rib. A film of July 1955 showed bilateral pseudarthrosis and increase of callus at the right rib (Fig. 2).

*Case* 2. Sister B., aged 16 years, had been employed for eighteen months at the time of examination in June 1954, and the radiograph showed a fracture of the first right rib with marked widening and fusiform callus on the medial aspect of the rib (Fig. 3). In January 1955 the break was more marked, particularly at the lateral part of the first right rib, and the fracture had a transverse double curved appearance. The radiological picture had not appreciably altered in July 1955, and in April 1956 the film showed an incompletely healed fracture of the first right rib (Fig. 4).

In both girls the fractures were at the same site in the region of the scalene tubercle and no other bony abnormality was shown in the thorax. At no time had the sisters any symptoms. They were the only children of the family, the mother suffered from a chronic type of pulmonary tuberculosis, otherwise the thorax of both parents was normal.

As it was thought that the lesion of the first rib in these sisters was due to long acting stress at work, nine female employees of two egg packing stations were examined. They were aged 16 to 35 years and did the same work as the sisters; in none of them was a fractured rib found. The Newcastle Mass Radiography Unit examined the employees of a third packing station; in this group six men did the actual lifting and no fracture was found.

## Discussion

These two sisters had been lifting heavy boxes without any symptoms, the younger one for the duration of eighteen months and the older girl for three years, when routine radiography revealed in the region of the scalene tubercle a fracture of the first right rib in the younger and of both first ribs in the elder girl; their age was 16 and 18 years at that time. The continuous strain at work must have exerted a regularly repeated sub-threshold stress upon their ribs. The first rib is flat and rather thin at the subclavian groove on the medial aspect of the bone. Indeed, at the time of the first examination in June 1954 the radiographs showed marked widening of the fracture line on the medial aspect of the first rib in girl B (Fig. 3) and of both ribs in girl A (Fig. 1), a feature which was also described by Powell (1950). During the action of heavy lifting, the first rib is fixed by the clavicle anteriorly and to a certain degree by the subclavian artery and the brachial plexus, while the scalenus anterior and medius muscles, inserted on each side of the subclavian groove, contract and, it is thought, may fracture the rib at the thinnest segment, namely the groove. However, none of the fifteen other persons exposed to the same occupational stress had fractured ribs, and it is reasonable to assume that the two sisters were constitutionally less well equipped than their workmates, and a disproportion existed between the inherent stability of the bone and the stability required to bear given stress. The stability of bone and the mechanism of fractures was investigated by Henschen (1932 and 1936) in collaboration with metallurgists. They examined the microscopical structure of normal and fractured bones, particularly in slowly occurring fractures, by physico-chemical methods and found changes of the crystal structure of the bones comparable

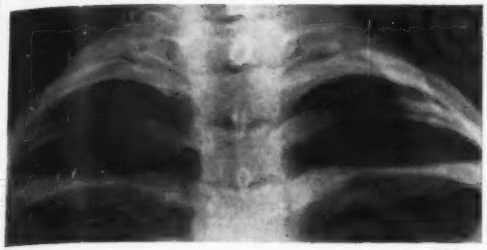

FIG. 1

Girl A. Fracture of both first ribs.

FIG. 1.—June, 1954.

FIG. 2.—July, 1955.

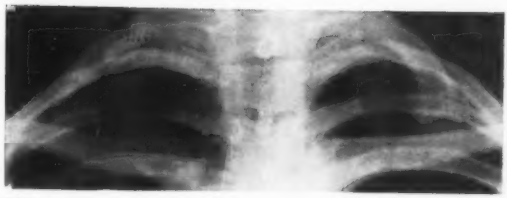

FIG. 2

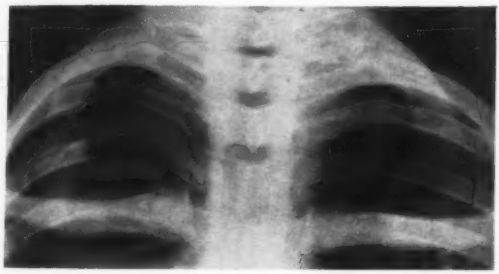

FIG. 3

Girl B. Fracture of first right rib.

FIG. 3.—June, 1954.

FIG. 4.—April, 1956.

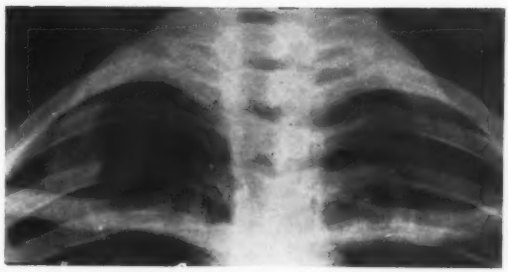

FIG. 4

*To face p. 256*

with fatigue structure in metals. Any conclusions going beyond this parallel can, however, not be drawn without teleological thinking as discussed by G. H. Bell (1956) in his paper " Bone as a mechanical engineering problem." Apart from the anatomical aspect of this problem in stress fracture, the functional element should be considered: clumsy incoordinate muscle action during work exerts a greater stress upon bone than a smooth action, and incoordinate action when frequently repeated may lead to lesion of the bone (Brandt, 1941). Unfortunately, it was not possible to watch the sisters at work and compare their movements with the movements of their workmates. The sisters were free from symptoms all the time and their case would compare with many of the stress fractures of the first rib discovered by Alderson and Powell among young men in the Services. Alderson observed the highest incidence in the age group of 15 to 20 years, the majority of Powell's cases were aged 18 to 19 years and all the fractures were in the region of the scalene tubercle. Jenkins' (1952) case was a boy of 16 years who sustained a fracture of the first right rib whilst lifting a heavy box to a counter, and at the same time a symptomless and older fracture of the first left rib without history of trauma was discovered.

A search of the literature revealed only six cases of fracture of the first rib in females and four of them occurring on the contralateral side following operation for thoracoplasty (Kohlbach, 1939; Sjoergen, 1942; Guggenheim and Cohen, 1948). Alderson detected no fracture of the first rib in the examination of 3,433 women serving in the Royal Navy and it is therefore, of particular interest that the two sisters affected had the same type of work and were exposed to the same stress. The occupational facts and radiological features of their bone lesions illustrate well the conditions and progress of stress fracture, a characteristic injury of youth. On checking the literature I found no similar case of stress fracture of the first rib in siblings of either sex.

## Summary

The case of symptomless fracture of the first rib in two young sisters, considered to be a stress fracture, is described. The features and the mechanism of this type of fracture are discussed and the relevant literature is reviewed.

Thanks are due to Dr. G. Hurrell, Director of the Newcastle-upon-Tyne Mass Radiography Unit, 1A, for the examination of employees of an egg packing station; and to Mr. M. James, Consultant Orthopædic Surgeon, Newcastle Group of Hospitals, for his advice.

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# AN OUTBREAK OF TUBERCULOSIS IN A SCHOOL

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## Introduction

A year-old infant died with tuberculous meningitis. The source of infection was found to be a woman whose work was in a day school. It was then realised that she was the likely source of infection in the case of two 4-year-old children who also suffered from tuberculosis but whose source of infection had so far not been traced.

The school was investigated by mass X-ray and tuberculin tests. The positive reactors were investigated further. A number of other cases of tuberculosis came to light and an estimate was made of the total number of pupils infected from the one source either clinically or subclinically.

From all the data accumulated an estimate was made of the relative incidence of bovine and human tuberculosis in the pupils of the school.

## The Outbreak

A 4-year-old boy developed a pleural effusion. Three months later another boy of the same age became ill with tuberculous meningitis. No source of infection could be found until a further three months had elapsed, when a 1-year-old boy died with tuberculous meningitis. He was found to have been infected by a woman (Mrs. X) who frequently visited the home. The two 4-year-olds were then linked with this woman, as they were pupils in the school where she worked and came into contact with her at dinner times.

The school has about 400 pupils. The Junior Department where the woman worked takes children of both sexes aged 4 to 8 years.

Mrs. X had been taken on as a temporary worker without any sort of medical examination. About sixteen months before she was proved to suffer from tuberculosis she had been ill with "influenza." Though she was soon back at work she was from that time obviously in failing health. In spite of suggestions by the teachers that she should see her doctor, she failed to do so, but when suspicion fell upon her she readily agreed to have an X-ray and shortly afterwards was admitted to hospital. The first case mentioned above occurred six months before she left the school and nine months after her influenzal illness.

## Radiographical Survey

Arrangements were quickly made for a mass radiography unit to be brought to the school and 339 pupils (85 per cent.) and all the teachers and domestic staff had chest films taken. The only positive findings were in 5 pupils. Two were treated for active primary chest infection and 3 were kept under surveillance.

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### Further Cases of Tuberculosis

Meanwhile, however, other cases appeared through the general practitioners and the hospitals. Two with erythema nodosum, 2 with pleural effusions and 3 active primary lung lesions. The last case presented three months after the open case had been segregated and nineteen months after her "influenza."

The total cases by then were 15. Thirteen of these were in the Junior Department of the school. One was a 13-year-old pupil in the Senior part of the school and one was the year-old infant who had died. All the pupils had dinner at the school.

### Tuberculin Survey

(1) *Jelly Tests.* It was thought that some estimate of the total pupils infected might be arrived at if a tuberculin survey was to be carried out. Tuberculin jelly was first used and 367 (92·4 per cent.) pupils were tested. The method used was as described in Ministry of Health Memorandum 1950. It is to be noted, however, that only those individuals were accepted as positive who showed gross vesiculation and/or gross erythma. Lesser reactions were recorded as doubtful.

*Results.* Positive 86 (21·9 per cent.); Doubtful 58 (14·6 per cent.); Negative 223 (56·4 per cent.).

(2) *Mantoux Tests.* In view of the doubtful results of Jelly tests obtained in 58 pupils a Mantoux test, using 0·005 mgm. P.P.D., was done on all except the definite positives. The method and reading was as set out in the aforementioned Memorandum.

*Results.* Out of 255 pupils tested (omitting those with strongly positive jelly tests) 43 had positive reactions and 212 negative.

Table I sets out all the results obtained by both tests. It is seen that the total positive in the school was 131 out of a total of 408 pupils. There remained 11 pupils who may have been positive—their jelly tests were doubtful—but Mantoux testing could not be carried out. The total positive reactors were, therefore, between 131 (33·7 per cent.) and 142 (36·8 per cent.) of pupils—*i.e.* about 35 per cent. The number of positives in each age group is seen in Fig. 1.

*Analysis.* Fig. 2 shows the percentage positive reactors in each age group. With the Clitheroe figures are plotted figures from other recent surveys. It is readily seen that there is a bulge in the 5 to 8-year-old age groups in Clitheroe as compared with the other areas. It is suggested that this represents approxi-

Table I

| | |
|---|---|
| Negative Jelly: Negative Mantoux .. .. .. | 143 |
| Negative Jelly: Mantoux not done .. .. .. | 34 |
| Negative Mantoux: Jelly not done .. .. .. | 38 |
| Negative Mantoux: Doubtful Jelly .. .. .. | 31 |
| Doubtful Jelly: Mantoux not done .. .. .. | 11 |
| Strongly positive Jelly: Mantoux not done .. .. | 74 |
| Positive Mantoux: Negative Jelly .. .. .. | 14 |
| Positive Mantoux: Doubtful Jelly .. .. .. | 17 |
| Positive Mantoux: Jelly not done .. .. .. | 12 |
| Known positives .. .. .. .. .. .. | 14 |
| Not tested .. .. .. .. .. .. .. | 20 |
| Total .. .. .. .. .. .. .. | 408 |
| Total Positive .. .. .. .. .. .. | 131 |

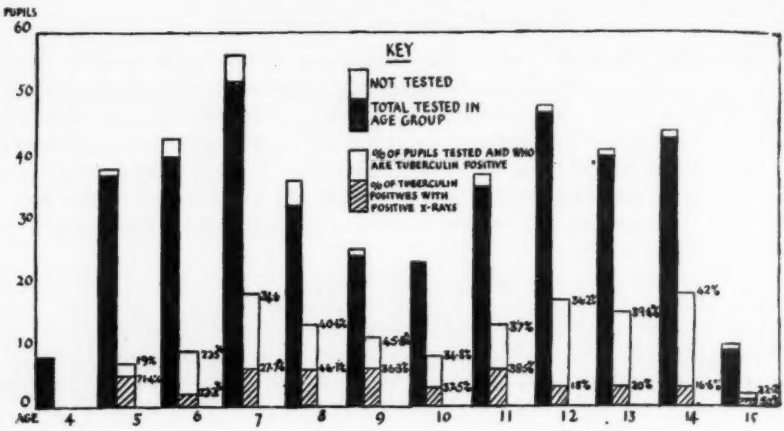


FIG. 1.—Distribution in age groups of positive reactors.

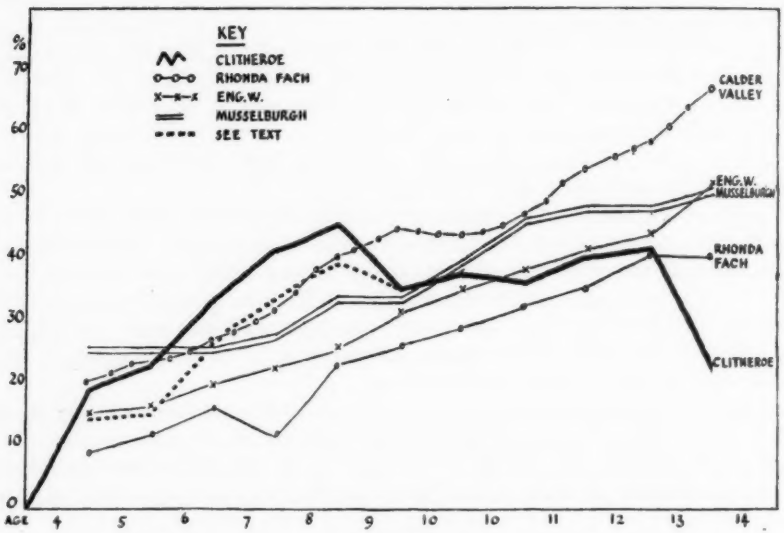


FIG. 2.—Tuberculin positive rates for Clitheroe school compared with other surveys.

mately the total number of pupils infected by the open case mentioned above. The known cases in this bulge zone totalled 13. The dotted line shows what the line would have been had these been subtracted. It does not by any means bring the line down to the average and it is estimated that about 17 more pupils must have been infected, making a total of about 30. (Later it will be seen that every effort was made to exclude other possible sources of infection which might have possibly contributed to the bulge.)

*Tuberculin rate compared with other areas.*

Recent surveys gave the following figures: Rhondda Fach (Jarman, 1953), 24 per cent.; England and Wales (M.R.C., 1952), 27·7 per cent.; Musselburgh (Murray *et al.*, 1955), 35·5 per cent.; Calder Valley (Keidan, 1952), 39 per cent. The figure in the Clitheroe school under review was 35 per cent.

*Comparison of Jelly testing and Mantoux.*

"Doubtful" results in this series include many who on normal readings of Jelly tests would have been called positive. In spite of this 31 pupils who had doubtful Jelly tests were negative when tested by Mantoux. In a further 17 instances where Jelly test was negative the Mantoux was positive. This shows a lack of correlation in 12·3 per cent. cases. The comparable figure in the Musselburgh survey was 6·5 per cent. This emphasises that there is a significant difference in the results of the two methods for testing.

*Chest X-rays in positive tuberculin reactors.*

Films were 5 in. × 4 in. All positive reactors not already under medical care had new films taken about nine months after the open case was discovered. The films were examined independently by two radiologists and one physician. A positive result was only accepted if so reported by two out of the three.

*Results.* Thirty pupils showed either enlarged hilar glands, a primary focus, or both. No active lesions were found. To this total were added the 13 pupils already known to have chest lesions. The total was then 43 pupils, which was 31.5 per cent. of positive reactors.

*How many positive reactions were due to bovine infection?*

It was thought that some estimate might be made of the amount of bovine infection if it were known—

(*a*) how many pupils had evidence of cervical and/or abdominal tuberculosis without any evidence of chest infection;
(*b*) to what extent and for how long pasteurised or T.T. milk was used;
(*c*) some history could be obtained from the parents on relevant points such as chronic cervical adenitis, chronic abdominal pain, unexplained illnesses, contact with human cases of tuberculosis and the area in which they lived.

To this end, therefore, one of us examined the pupils for evidence of tuberculous infection in the neck. This was done when they attended for X-ray. In addition a 5 in × 4 in. film was taken of the abdomen of all positive reactors. When the results of tuberculin test, X-rays of chest and abdomen were known, the parents were invited to attend at the school. The object of the investigation was explained and the results to date given to them regarding their own child. They were then questioned along the lines set out above.

*Results.* The parents or guardians of 95 out of the 135 positive reactors attended. On a further 12 we already had relevant information.

*Milk.* It was found that 50 of the families out of 95 were taking safe milk—either T.T. or pasteurised.

*Cervical adenitis.* In 10 cases the child had suffered from persistent cervical adenitis. Four had glands in the neck which could clinically have been tuberculous. Two had been operated upon for tuberculous glands. Six of the cases had X-rays which showed calcified hilar glands, and 1 had calcified glands in the abdomen. Two had a history of chronic abdominal pain.

*Chronic abdominal pain.* Twelve parents gave such histories of their children. Two had chronic cervical adenitis, yet each had negative chest and abdominal X-rays. Only 1 showed calcified abdominal glands, but 5 showed calcified hilar glands. Two others had been in hospital on account of abdominal pain. One had an appendicectomy and another had calcified abdominal glands on X-ray.

*History of contact with human tuberculosis (excluding the school case, Mrs. X).* Four pupils came from a hostel where they were cared for because their mother suffered from tuberculosis. These were all between 12 and 15 years old and not—it will be noted—in the Junior School. Five pupils had been in contact with a Mrs. N. who had been in a sanatorium for two years and was still there. These were aged 5, 6, 8, 8, and 11 years. Four of these attended Junior School and all had evidence of recent infection, and it was thought that perhaps school infection was as likely as infection from Mrs. N. Two other pupils had been in contact with known tuberculosis outside the school and in each case chest X-rays were negative in this investigation.

*History of previous chest trouble.* In 17 cases there was a history of bronchitis or asthma.

*Unexplained illnesses.* This part of the enquiry, as might be imagined, was not very fruitful. Doctors usually find some explanation for the parents' benefit even if the cause of an illness is, in fact, not known.

There were 7 pupils to consider. Six pupils had illnesses about the same time as known cases in this outbreak. Three had hilar gland enlargement on X-ray. Another had a negative X-ray, but his siblings all had hilar gland enlargement. One had no evidence of primary infection apart from positive Mantoux, and another had recurrent illnesses and seemed unlikely to have had a primary illness. One only had calcified abdominal glands.

*X-ray of abdomen*

In 9 pupils calcified abdominal glands were demonstrated. They were in all the various age groups and not predominantly in the Junior School.

## Discussion

It is realised, of course, that there is some doubt still about the significance of cervical adenitis in some cases. Many agree with Calmette and Behring that the disease is part of a primary complex, the primary focus being in the nasopharynx. Others think that neck glands may become infected by lymphatic spread from a lung complex. Yet others believe that hæmatogenous spread is responsible for cervical gland involvement.

That tuberculous adenitis is disappearing where safe milk is consumed strongly suggests that most cases are in fact bovine in origin. This has recently been emphasised (Letham, 1955). He says: " The all too common ailment of

childhood 'glands in the neck,' once an accepted feature of English life, has disappeared." This is, of course, an overstatement. It is, however, true in areas where only safe milk is sold. In the Clitheroe area cases are still seen, though with diminishing frequency.

There are, however, cases where there can be no reasonable doubt that cervical glands have become infected from lung infection. Conversely, spread may also go the other way—from neck to hilar glands. It was therefore decided to eliminate any case which showed any evidence of chest infection.

Taking into account all the evidence, it was thought that 23 pupils with positive tuberculin reactions could be placed in the group of probable bovine infections. They showed evidence of cervical or abdominal tuberculosis without any evidence of chest involvement and had taken "unsafe" milk.

Of these 23 cases, 9 came from the town and 14 from the rural area.

When the whole school was divided there were found to be 281 pupils from the town and 127 from the rural area. The positive reactors were 32·3 per cent. and 31·5 per cent. respectively.

In a similar way it was found that there were 9 cases in the rural area which were, so far as could be ascertained, solely pulmonary infections, and in the town 41 cases.

There remained 22 and 36 cases in the respective areas which were somewhat equivocal and, therefore, unclassified. They were allocated proportionately.

The proportion of tuberculin positives due to bovine infection is suggested thus:

TABLE II

| | *Rural* | *Urban* |
|---|---|---|
| Total pupils | 127 | 281 |
| Tuberculin positive | 40 (31·5%) | 91 (32·3%) |
| Probably respiratory (human) | 9 (22·5%) | 41 (45%) |
| Probably non-respiratory (bovine) | 9 (22·5%) | 14 (15·4%) |
| Unknown | 22 | 36 |
| Unknown allocated proportionately: | | |
| Respiratory | 11 | 27 |
| Non-respiratory | 11 | 9 |
| New totals on above assumptions: | | |
| Respiratory | 20 (50%) | 68 (74·5%) |
| Non-respiratory | 20 (50%) | 23 (25·5%) |

It is thus suggested that in the rural area about half the positive tuberculin reactions are due to milk infection and half to human infection. In the town, on the other hand, about a quarter only are bovine and three-quarters are human.

### ACTION TAKEN AS A RESULT OF THE SURVEY

B.C.G. vaccination was offered to Mantoux-negative 13-year-olds and was accepted by all. As a result of requests from parents some 14-year-olds were also vaccinated.

*Conclusions*

The results of this investigation once again underline the fact that an open case of tuberculosis in contact with young children is a very great danger. There is a growing awareness that it is desirable to have X-rays taken at regular intervals in the case of teachers. There is much less care taken in selection of part-time workers. For one reason or another there is a big turnover of such workers and many escape even the most superficial examination. Especially is this true of those taken on temporarily. Yet even these individuals frequently come into close contact with the pupils and more especially the younger ones. These, of course, are the most susceptible to tuberculous infection and to its most dangerous complications. It cannot, therefore, be stressed too strongly that such workers should be subjected to proper medical examination and it would not appear too difficult to arrange X-ray examinations through the mass radiography units or in the general hospitals using 5 in. × 4 in. films.

It has been maintained by some that when teachers are X-rayed in a general hospital as a condition of their employment or as part of an examination for superannuation, payment is due to the Hospital Management Committee or to the Radiologist, these examinations not being within the scope of the National Health Service. It seems doubtful, however, whether payment can be demanded, where the examination is solely for the protection of the pupils as would usually be so in the case of domestic workers.

## Summary

Fifteen cases of primary tuberculosis in school children which presented within a twelve-month period were attributed to contact with a school meals attendant who proved to be an open case of pulmonary tuberculosis. One child under school age died as a result of tuberculous meningitis believed to have been contracted from the same woman. The subsequent investigation of the school is described and evidence produced which suggests that about 30 pupils in all were infected by the 1 open case.

Evidence is presented which suggests that in the pupils living in the town tuberculous infection was acquired from human contact three times more frequently than from milk. In the surrounding rural area, on the other hand, it was contracted from milk as frequently as from human contact.

The need for adequate medical examination of all who work in schools is stressed.

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# THE COMBINED USE OF ISONIAZID AND NUPASAL-213 IN PULMONARY TUBERCULOSIS

## A STUDY OF THE TOXIC EFFECTS AND THE DEVELOPMENT OF CROSS-RESISTANCE BETWEEN ISONIAZID AND NUPASAL-213 IN THE TREATMENT OF PULMONARY TUBERCULOSIS

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In the treatment of tuberculosis, Streptomycin, para-amino-salicylic acid (PAS) and Isonicotinic acid hydrazide (INAH) are the present-day drugs of choice. Each has the disadvantage however that, if given alone, resistant tubercle bacilli sooner or later develop. It is the practice therefore that no single drug is given alone, but always in combination with one or both of the other two. INAH given by mouth is a safe drug, and in the usual doses of 200 mg. daily produces few toxic effects. When the dose is increased to 300 mg. or more per day, some cases develop peripheral neuritis. There are few other drawbacks to its use, but it must be given in combination with other tuberculostatic drugs.

Investigations into related chemical compounds produced in 1952 o-hydroxybenzal iso-nicotinyl hydrazone. This is a yellow crystalline substance formed by the interaction of isonicotinic acid hydrazide and salicylaldehyde and purified by repeated re-crystallisation from ethyl alcohol. On a gravimetric basis it contains slightly over 50 per cent. isoniazid nucleus. The drug was first produced by the firm of Smith and Nephew, and having been shown to have a high *in vitro* activity against *Myco. tuberculosis* by Bavin, Drain, *et al.* (1952), was marketed under the trade name of Nupasal-213. In the U.S.A. it was manufactured by the Nepera Chemical Co. of New York under the trade name of Salizid, and in that country its use in clinical trials was reported by Conalty (1953) and Barry and Conalty (1954). Other studies by Hart *et al.* (1954), Katz *et al.* (1954), Nagley (1954), Ewart *et al.* (1955) and McCormick *et al.* (1955) confirmed the tuberculostatic effect of the drug. Katz and his co-workers used doses of 200 to 400 mg. daily for a period of four to six months. Treatable patients showed a favourable response, but in advanced cases sputum conversion was nil, and of those patients who were known to have drug-sensitive tubercle bacilli at the start of the study, 50 per cent. had drug-resistant bacilli by the sixth month. Growth on medium containing 1 mc.gm. per ml. of the drug

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was taken to show resistance. In the study by Ewart *et al.* (1955), doses up to 1,200 mg. daily were given with no evidence of neurotoxicity or liver damage. Cases resistant to INAH were not benefited by larger doses of Salizid (Nupasal-213). Nagley in his trial used doses of 1,000 to 1,200 mg. daily and combined the drug with Streptomycin and PAS. The Veterans Administration (1956) found no evidence of neurotoxicity on a régime of 1,200 mg. daily. Many other workers, principally American, have contributed to the literature on o-hydroxybenzal isonicotnyl hydrazone.

On the laboratory side, Bavin, James, *et al.* (1955) showed that Nupasal-213 after oral administration was broken down, at least in part, to form INAH. Working with rabbits, the drug was shown to have a tuberculostatic activity of the same order as INAH with only $\frac{1}{10}$ to $\frac{1}{8}$ of the toxicity of INAH. *In vitro* the use of the combined drugs Nupasal-213 and INAH was reported to delay the emergence of bacilli resistant to either drug.

Somewhat similar results were reported by Steenken, Wolinsky and Montalbine (1954). These workers reported that while the H37Rv strain of tubercle bacillus was easily made resistant to Salizid (Nupasal-213) by serial passage in drug-containing medium, the rate at which this developed could be slowed by using medium containing both INAH and Salizid.

If the two drugs could be given together safely in suitable doses and without the development of cross-resistance it would be a great help in dealing with the problem of the chronic sputum-positive case, as the drugs given separately are well tolerated and have none of the unpleasant side effects of PAS. One of us (J.C.) has found that a dose of Nupasal-213 of 1,500 mg. daily is well tolerated by patients not receiving INAH.

## Investigation

The present investigation was divided into three parts: (1) a therapeutic trial, (2) an *in vitro* test for cross-resistance, and (3) an animal (guinea-pig) test for cross-resistance.

In the therapeutic trial the drugs were given to a test group in the dose of 200 mg. of INAH plus 1,600 mg. of Nupasal-213 daily. Two tablets each containing 50 mg. INAH and 400 mg. Nupasal-213 were given twice daily. The object of this part of the investigation was to see if the combination of the drugs would prevent the emergence of tubercle bacilli resistant to either drug, and to see if any toxic effects were manifested by the combined use of these closely related drugs, each given in their usual dose. To a control group were given 10 g. PAS and 200 mg. INAH daily in the form of Pycamisan cachets. (Some of the control group received in addition Streptomycin intramuscularly for five days a week.) The cases chosen were chronic cavitary cases of pulmonary tuberculosis of at least a year's standing in whom there was not much likelihood of radiological improvement or sputum conversion with intensive drug therapy, and in whom surgical intervention was not possible. The subjects were over 18 years of age, and most had had various courses of treatment with combinations of Streptomycin, PAS and INAH in the past. As suitable cases appeared at the Clinic for routine review they were placed alternately in the test and control group.

At the start of the trial, tubercle bacilli sensitive to 1 mc.gm./ml. of Nupasal-213, INAH and 3 mc.gm./ml. Streptomycin, and to 10 mc.gm./ml. of PAS, were isolated from all cases. Monthly review of each cases was undertaken, and sputum cultures and sensitivity tests were done each month for six months. Nineteen persons were entered into each group. In the test group three persons, and in the control group six persons, failed to complete the trial for non-medical reasons.

Table I shows the different toxic effects noted.

TABLE I

| *Nature of toxic effect* | *Number of cases* | |
|---|---|---|
| | *Test group* | *Control group* |
| Neuritis .. .. .. .. .. .. .. | 5 | — |
| Epilepsy .. .. .. .. .. .. .. | 1 | — |
| No toxic effect .. .. .. .. .. .. | 10 (16) | 12 (12) |

Table II shows the final sputum state.

TABLE II

| *Sputum state* | *Number of cases* | |
|---|---|---|
| | *Test group* | *Control group* |
| Sputum-positive and still sensitive .. .. .. .. | 5 | 2 |
| Sputum-positive and resistant .. .. .. .. | 9 | 2 |
| Sputum negative .. .. .. .. .. .. | 2 (16) | 8 (12) |

One case in the control group died of tuberculosis.

In the second part of the investigation the tubercle bacilli isolated from twelve patients known to be resistant to 50 mc.gm./ml. of INAH were inoculated on to medium containing 0·2, 1, 5, 10, and 50 mc.gm./ml. respectively of Nupasal-213. The patients concerned had never received Nupasal-213 so far as was known, and the twelve different strains of bacilli had all been isolated before Nupasal-213 appeared on the market in this region. Of the twelve different strains, nine showed resistance to 50 mc.gm./ml. of Nupasal-213, and the growth was confluent with all nine strains. One strain was sensitive to 50 mc.gm./ml. but resistant to 10 mc. gm./ml. and 2 strains were sensitive to 10 mc.gm./ml. but resistant to 5 mc.gm./ml.

For the third part of the investigation, three different strains of tubercle bacilli were used. These, as in the second part of the investigation, were from patients who had never received Nupasal-213 but had received INAH. Two strains were resistant to 50 mc.gm./ml. of INAH and the third was resistant to 10 mc.gm./ml. Twelve mature guinea pigs were selected and divided into three groups, four animals to each strain of tubercle bacillus. All the guinea pigs were given a normal diet but, in addition, the first animal of each group

was given INAH, the second was given INAH and Nupasal-213, the third was given Nupasal-213, and the fourth no drugs. The dose of each drug, or combination of drugs, was calculated on a weight basis in relation to the adult human dose administered in the therapeutic trial, and the drugs were given orally through a pipette. Each animal was given approximately 100 viable tubercle bacilli intraperitoneally. All the animals were killed and examined within six weeks. All showed extensive tuberculosis.

## Discussions and Conclusions

The animal experiment shows that in guinea pigs neither Nupasal-213 alone, nor the combination of Nupasal-213 and INAH, will cure a guinea pig infected with virulent human INAH-resistant tubercle bacilli.

Barry and Conalty have already shown that a combination of equal parts of INAH and Salizid (Nupasal-213) was completely ineffective at a dose of 96 mc.gm./kg. in mice infected with INAH-resistant strains of tubercle bacillus.

The *in vitro* experiment with twelve strains of tubercle bacilli strongly resistant to INAH shows that nine of the strains were equally resistant to Nupasal-213. In three cases Nupasal-213 was more bacteriostatic, but the difference is not great and all twelve strains are considered to be resistant to Nupasal-213.

When the therapeutic trial part of the investigation is considered it may be argued that, as most of the patients had received varying amounts of Streptomycin, PAS and INAH before entering the trial, and although preliminary sensitivity tests showed the tubercle bacilli isolated to be sensitive to these drugs, some of the organisms may have been reaching a critical threshold where they were about to show resistance levels. This of course would apply equally to the control group, and as the cases were picked at random the groups may be taken to be evenly matched in this respect.

Of the sixteen persons receiving combined Nupasal-213 and INAH, nine eventually produced tubercle bacilli resistant to both drugs. In the control group, only two of the thirteen cases developed resistant bacilli.

Table III shows the time taken for resistance to develop and the degree of resistance to each drug.

TABLE III

| *Test case* | *Control case* | *Drug régime* | *Time in months to develop resistance* | *Level of resistance* | |
|---|---|---|---|---|---|
| | | | | *INAH* | *Nupasal* |
| | | | | *mcg./ml.* | *mcg./ml.* |
| 1 | | INAH and Nupasal | 5 | 50 | 5 |
| 2 | | " " " | 6 | 50 | 50 |
| 3 | | " " " | 4 | 5 | 10 |
| 4 | | " " " | 2 | 50 | 50 |
| 5 | | " " " | 1 | 5 | 5 |
| 6 | | " " " | 4 | 50 | 50 |
| 7 | | " " " | 4½ | 50 | 50 |
| 8 | | " " " | 4 | 5 | 10 |
| 9 | | " " " | 6 | 50 | 50 |
| | 1 | P.H. (10) | 6 | 50 | 50 |
| | 2 | P.H. (10) | 5 | 50 | 10 |

The development of neuritis from the combined Nupasal-213 and INAH therapy is of interest. In many hundreds of cases of tuberculosis treated with a daily dosage of 200 mg. of INAH we have never seen this complication. Nor has it been seen in some thirty cases treated with 1,500 mg. Nupasal-213 (six 250-mg. tablets) daily. On combined INAH and Nupasal-213 therapy neuritis developed in five patients at 1½, 2, 2, 3 and 4 months respectively. The drugs were discontinued in four instances at the first sign of neurotoxicity and pyridoxine was administered. This gave quick remission of symptoms. On one case only was it not possible to continue the drugs to the end of the six months of the trial. In that case where neuritis developed at one and a half months there was also an erythematous rash on the forearms and legs. One of the therapeutic series was an epileptic. After a few days of the combined drugs he had a violent fit followed by sickness. This recurred with a few more doses of the drugs which had to be discontinued. Katz, Georges, *et al.* (1956) mention an increased seizure frequency in two epileptics on Salizid. Barborik and Weidermann (1955) mention fourteen epileptiform fits having appeared at ten to fifteen minutes intervals in a patient who attempted suicide by taking 3 to 10 g. of INAH.

The combination of INAH and Nupasal-213 in the dosage used in the trial is considered not to be safe for routine clinical use.

Sputum conversion was less in the therapeutic group. Two of the test group showed sputum conversion against eight in the control group. Although cavitary cases were picked in whom it was thought there would be no conversion of the sputum, it does show what can be achieved in chronic cases The small number of conversions in the test group is attributed, in the main, to the fact that many of the patients did not complete six months on the drugs, because of the development of (*a*) neurotoxicity and (*b*) resistant organisms.

From this work it is concluded that for all practical purposes Nupasal-213 (Salizid) and INAH are identical in their action. Neither drug will prevent tubercle bacilli from becoming resistant to the other to the same degree that Streptomycin or PAS will delay the emergence of INAH resistance. While doses of 200 mg. INAH or 1,600 mg. Nupasal-213 daily are safely tolerated when taken alone, in combination there is a very real danger that neurotoxic symptoms will develop. Either drug is a very potent anti-tuberculosis agent, but each should be used concurrently with Streptomycin or PAS or some other unrelated drug.

Nupasal-213 and INAH used together in the doses above mentioned are no substitute for accepted therapeutic régimes with two different drugs when dealing with chronic sputum-positive cases of pulmonary tuberculosis. The real dangers arise when the market becomes flooded with drugs, and two preparations which may be closely related chemically but bear unrelated trade names are used unwittingly together.

## Summary

A study was made of o-hydroxybenzal isonicotinyl hydrazone (Nupasal-213 or Salizid) in combination with isoniazid in treating cases of pulmonary tuberculosis. Neither drug can guard against the tubercle bacilli becoming resistant to the other.

Control cases treated with isoniazid and streptomycin and PAS developed resistance to isoniazid much less readily than the cases in the therapeutic trial, and it is concluded that treatment on these accepted lines is the treatment of choice in dealing with chronic, sputum-positive case of pulmonary tuberculosis with sensitive organisms.

Cases on combined isoniazid and Nupasal-213 in the dosage used showed a high incidence of neurotoxic symptoms.

Experiments with guinea pigs showed that neither Nupasal nor a combination of Nupasal and Isoniazid will keep alive or cure an animal infected with virulent Isoniazid-resistant organisms.

Isoniazid-resistant tubercle bacilli grew readily on media containing Nupasal-213 in full strength.

As far as clinical use is concerned Nupasal-213 (Salizid) and isoniazid are identical. They should not be used alone or together without the addition of anti-tuberculosis drugs of different chemical structure.

We are indebted to the firm of Smith and Nephew, who supplied the combined tablets of Nupasal-213 and Isoniazid which were used in this investigation.

Thanks are also due to Mr. W. C. House, F.I.M.L.T., of the Victoria Sectoral Bacteriological Laboratory, Glasgow.

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# TUBERCULOSIS IN THE POTTERY INDUSTRY

## BASED ON MASS RADIOGRAPHY INVESTIGATIONS

By E. Posner

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"The word pottery is of a very elastic character and may be extended to mean any workman employed in the industry. The operations differ widely in hygienic conditions."

J. Arlidge (1892).

More than 80 per cent. of British pottery is manufactured in Stoke-on-Trent. This unique concentration made it possible to radiograph the large majority of all pottery workers in this country between 1952 and 1955.

This paper attemps to compare the prevalence rates of active tuberculosis in workers exposed to dust in the various branches of the industry and in those pottery operatives who are not affected by dust.

In the main sections of the industry, shown on Table 1, only few workers—flint millers—are exposed to the risk from pure silica dust. The following table shows, however, that the materials used for making general earthenware contain a large proportion of free silica in the form of powdered and calcined flint. On the other hand, bone china contains very little free silica.

| *General Earthenware* | *Per cent.* | *Bone China* | *Per cent.* |
|---|---|---|---|
| Blue ball clays (kaolinites) .. | 18-47 | China clay .. .. | 20-30 |
| China clay (kaolinites) .. .. | 24-37 | Bone ash .. .. | 27-46 |
| Flint (free silica) .. .. .. | 21-38 | Cornish stone .. .. | 20-32 |
| Cornish stone (felspar and quartz) | 7-15 | | |

(Rosenthal, 1949.)

The materials used for making dust tiles, sanitary earthenware and electrical porcelain are very similar to those of general earthenware. Rockingham and jet ware is in the form of brown teapots, made from local marls which contain little free silica.

Only the makers of general earthenware, sanitary earthenware and electrical porcelain are therefore exposed to dusts containing a significant proportion of free silica. The exposure to silica-containing dust is only minimal for bone china makers. Furthermore, fine quartz sand is used in the earthenware sections for the placing of articles during the first or "biscuit" firing. Dippers who glaze the ware after second firing are exposed to the dust of dried silica-containing glazes.

It is noteworthy that a large proportion of workers manipulate the ware in a state where no dust is encountered—for instance, decorators, packers, sorters and maintenance personnel.

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TABLE I.—RESPONSE TO MASS RADIOGRAPHY IN NORTH STAFFORDSHIRE POTTERY INDUSTRY, 1952-55, ACCORDING TO INDUSTRIAL SECTIONS

| *Industrial sections* | *MEN* | | | *WOMEN* | | | *PERSONS* | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Employed* | *X-rayed* | *Per cent.* | *Employed* | *X-rayed* | *Per cent.* | *Employed* | *X-rayed* | *Per cent.* |
| Potters' millers .. | 593 | 453 | 76·4 | 35 | 24 | 68·6 | 628 | 477 | 75·9 |
| General earthenware | 10,916 | 7,956 | 72·9 | 20,654 | 15,486 | 74·9 | 31,570 | 23,442 | 74·2 |
| Bone china .. .. | 2,488 | 1,606 | 64·5 | 5,927 | 3,905 | 73·7 | 7,785 | 5,511 | 70·8 |
| Dust tiles .. .. | 3,469 | 2,501 | 72·1 | 3,701 | 3,386 | 91·5 | 7,170 | 5,887 | 82·1 |
| Sanitary earthenware | 2,055 | 1,277 | 62·1 | 663 | 380 | 57·3 | 2,718 | 1,657 | 60·9 |
| Electrical porcelain | 1,728 | 1,174 | 67·9 | 2,643 | 1,588 | 60·1 | 4,371 | 2,762 | 63·2 |
| Rockingham and jet ware | 673 | 462 | 68·6 | 901 | 689 | 76·5 | 1,574 | 1,151 | 73·1 |
| All sections .. | 21,922 | 15,429 | 70·4 | 33,894 | 25,458 | 75·1 | 55,816 | 40,887 | 73·2 |

## EARLIER INVESTIGATIONS

The high mortality from pneumoconiosis and tuberculosis in pottery workers has been shown by Meiklejohn (1949a) and by the Occupational Mortality reports of the Registrar-General. A Home Office investigation (Sutherland and Bryson, 1926; Home Office, 1928) proved that, apart from flint workers, the much larger groups of earthenware makers and placers were exposed to a considerable pneumoconiosis risk. Statutory periodical examinations of certain categories of workers were introduced in 1931 (Home Office, 1931-39). They applied, however, only to a relatively small number of all workers and did not always include radiographic examination (Meiklejohn, 1950). The results, therefore (Meiklejohn, 1947, 1949a), cannot be compared with the present series, which is much less selective.

## THE PRESENT INVESTIGATION

*Response.* Workers of 219 out of 230 factories were X-rayed in organized groups at their works. The laborious method of visiting many small industrial units, rather than relying on a few central points of concentration, seems to have paid dividends, as the response in all factories but one was above 60 per cent. This compares well with the experience in Salford, where in 104 out of 266 factories less than 50 per cent. accepted radiographic examination (Goodman and Bradshaw, 1957). Table I shows the acceptance rates in the various sections of the industry. In the important general earthenware and bone china section, the response was above 70 per cent. and the response by female tile makers was exceptionally good.

For the purposes of this paper it is fortunate that the sex and age specific response by workers exposed to dust in the earthenware and in the china industries were very similar. The same applies to workers without dust hazard (Fig. 1). The graphs in the figure are based on accurate employment data, furnished by thirteen representative earthenware and china factories. In both the earthenware and china sections the acceptance rates of workers exposed to dust hazard (makers and placers) were highest in young operatives and main-

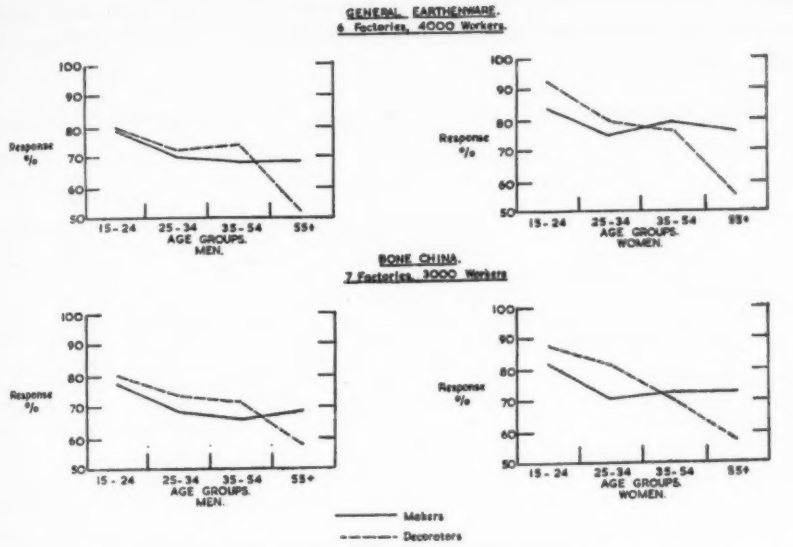


FIG. 1.—Age and sex specific response by makers and decorators in earthenware and china industry.

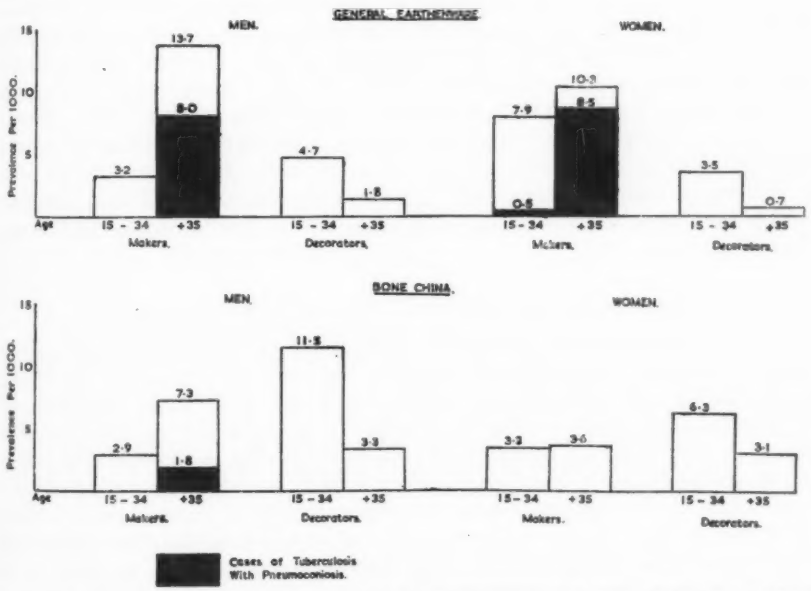


FIG. 2.—Age specific prevalence of tuberculosis. Earthenware and china industry. Makers and decorators.

tained a fairly stable level of about 70 per cent. in middle-aged and elderly workers. In contrast the response by decorators showed a steady decline with higher age.

TABLE II.—PREVALENCE OF ACTIVE TUBERCULOSIS IN POTTERY INDUSTRY, ACCORDING TO INDUSTRIAL SECTIONS

| *Industrial sections* | *MEN* | | | *WOMEN* | | |
|---|---|---|---|---|---|---|
| | *X-rayed* | *Cases of active Tb.* | *Per 1,000* | *X-rayed* | *Cases of active Tb.* | *Per 1,000* |
| Potters' millers .. .. .. | 453 | 5 | 11·0 | 24 | — | — |
| General earthenware (including earthenware and china) | 7,956 | 43 | 5·4 | 15,486 | 69 | 4·4 |
| Bone china .. .. .. .. | 1,606 | 12 | 7·5 | 3,905 | 21 | 5·4 |
| Dust tiles .. .. .. .. | 2,501 | 9 | 3·6 | 3,386 | 10 | 2·9 |
| Sanitary earthenware .. .. | 1,277 | 10 | 7·8 | 380 | 1 | 2·6 |
| Electrical porcelain .. .. | 1,174 | 6 | 5·1 | 1,588 | 5 | 3·1 |
| Rockingham and jet .. .. | 462 | 3 | 6·5 | 689 | 3 | 4·3 |
| Total .. .. .. | 15,429 | 88 | 5·7 | 25,458 | 109 | 4·3 |

## RADIOGRAPHY AND ASSESSMENT OF FILMS

The standard 35 mm. technique was used and the films were viewed by the author throughout the whole period. The existence of observer errors by single readers must now be accepted (Yerushalmy *et al.*, 1950; Cochrane and Garland, 1952; Clayson *et al.*, 1955) and there can therefore be little doubt that in this series, as in all investigations based on the same technique, some small genuine lesions were missed and that the prevalence rates err on the side of understatement. However, the results seem to be comparable *inter se*, as all films were interpreted by the same reader, whose accuracy or inaccuracy is unlikely to have been significantly different at the different stages of the survey. It should also be mentioned that clay workers and decorators attended mostly in mixed groups.

All persons whose 35-mm. film suggested significant lesions were recalled for full-sized films, which were assessed independently by the author and by the chest physicians.

## DIAGNOSTIC CRITERIA OF "ACTIVE" TUBERCULOSIS

In this connection the term active tuberculosis is used in those cases which the area chest physicians classified as tuberculosis, A or B, I, II, III, according to the classification of the Ministry of Health. In addition, many cases referred to the chest clinics were diagnosed as pneumoconiosis with progressive massive fibrosis, but these are not included into this analysis. The difficulties of differential diagnosis between the early forms of P.M.F. and active tuberculosis are very considerable, and have been recently discussed as regards coal workers by Cochrane *et al.* (1956). Generally, it can be said that the chest physicians diagnosed active tuberculosis in doubtful cases, only in the presence of a positive sputum or of marked clinical signs, such as a high B.S.R., loss of weight, or rapid spread of the lesion.

## Results

Table II shows the sex specific distribution of active tuberculosis in the different sections of the pottery industry. The 197 cases give a prevalence rate of 5·7 per thousand for men and 4·3 per thousand for women. The case-finding rates for men were well above the average in flint mills, in the sanitary earthenware section and in bone china manufacture, and fell considerably short of the average for women in the dust tile and electrical porcelain industry.

Table III.—Prevalence of Tuberculosis in Flint Processes of Pottery Industry

| | *X-rayed* | *Cases of active Tb.* | *Rate per* 1,000 | *Number of cases over the age of* 35 |
|---|---|---|---|---|
| Male china biscuit placers and odd-men biscuit placers | 267 | 2 (2) | 7·5 | 2 |
| Female china biscuit brushers and sorters | 296 | 4 (4) | 13·5 | 3 |
| Male flint millers and mill labourers.. | 261 | 4 (3) | 15·3 | 2 |

Figures in brackets are cases of pneumoconiosis with active tuberculosis. They are included into the total and not additional.

*General Earthenware and Bone China Industry*

For these two main sections of the pottery industry the marked differences in prevalence rates according to dust exposure and to age are shown in figure 2. The case finding rates in middle-aged and elderly earthenware makers were significantly higher than those of decorators and maintenance personnel of corresponding age. Also young female earthenware makers produced a proportionally much larger number of cases than young decorators. The high rates in middle-aged and old earthenware makers were almost entirely due to cases of tuberculosis with radiological evidence of pneumoconiosis. Amongst female clay workers, the highest rates (15·3 per thousand) were found in "towers" who fettle the edges of the dry ware before firing. (Posner, 1956). The findings in the bone china industry, where the dust encountered by makers contains only little free silica, were quite different. With the exception of middle-aged male makers, the case finding rates in decorating departments were the same or higher than in making shops.

*Flint Processes*

The serious mortality from silicosis and tuberculosis in china placers and female biscuit warehouse workers, who in the past used pure flint for "bedding" the ware for first or "biscuit" firing, led to the gradual substitution of alumina powder for flint. The change over was completed in all factories by 1944. No cases of active tuberculosis were found in workers who had been exposed to alumina dust only. All cases of tuberculosis, shown in Table III had worked with flint for periods ranging from 5-30 years.

*Dust Tiles*

These are die-pressed and fettled mostly by women who, in pre-war days, showed a high prevalence of silicosis and tuberculosis. Because of this, they are to-day the only group of female pottery operatives scheduled for periodical

examinations under the Silicosis and Asbestosis (Medical Arrangement) Scheme. Contrary to expectations, the present examinations produced only low rates of tuberculosis in young tile-makers and no cases were found in middle-aged or elderly women, a marked contrast to female earthenware clay-workers, (Table IV).

TABLE IV.—ACTIVE TUBERCULOSIS IN SOME GROUPS OF FEMALE POTTERY WORKERS AND WOMEN, NOT CONNECTED WITH POTTERY INDUSTRY
Stoke-on-Trent, 1952-55

| | − 35 YEARS | | | + 35 YEARS | | | TOTAL | | |
|---|---|---|---|---|---|---|---|---|---|
| | *X-rayed* | *Active tuber-culosis* | *Rate per 1,000* | *X-rayed* | *Active tuber-culosis* | *Rate per 1,000* | *X-rayed* | *Active tuber-culosis* | *Rate per 1,000* |
| General earthenware makers | 2,016 | 16 | 7·9 | 2,333 | 24 | 10·3 | 4,349 | 40 | 9·2 |
| Bone china makers .. | 612 | 2 | 3·3 | 548 | 2 | 3·6 | 1,160 | 4 | 3·4 |
| Dust tile makers and fettlers | 706 | 3 | 4·2 | 379 | — | — | 1,085 | 3 | 2·8 |
| Earthenware and china decorators | 7,105 | 29 | 4·1 | 5,279 | 7 | 1·3 | 12,384 | 36 | 2·9 |
| Women in Stoke-on-Trent, not connected with pottery industry | 6,298 | 22 | 3·5 | 3,756 | 4 | 1·1 | 10,045 | 26 | 2·6 |

*Sanitary Earthenware*

In this section, efficient dust extraction has always been a difficult technical problem (Chief Inspector of Factories, 1951) and sanitary casters are known to be subject to a considerable pneumoconiosis risk. Six of the ten cases of tuberculosis in men were sanitary casters, a prevalence rate of 14.3 per thousand. In four cases, there was definite radiological evidence of pneumoconiosis.

*Electrical Porcelain*

With the exception of one female clerk, all cases were workers who had been exposed to silica-containing dust in the manufacture of electrical insulators and switches, or had in the past used flint for placing.

*Rockingham and Jet*

Only one case was found among makers of brown teapots. The other five cases were packers, placers and members of the staff.

## Discussion and Conclusions

In the past, radiographic group examinations in the pottery industry reached only a relatively small number of workers selected by age, sex and occupation. The introduction of mass radiography has now made the assessment of tuberculosis in the industry as a whole easier and more accurate.

The high prevalence of tuberculosis in middle-aged and elderly flint and earthenware clay workers in this series was to be expected, and here the findings confirm the close relationship between silicosis and tuberculosis. On the other hand, bone china makers produced prevalence rates considerably lower than

those of earthenware makers and little different from those of earthenware and china decorators.

With regard to an occupational analysis, the figures shown here for women are likely to be more accurate than those for men, whose industrial histories were in many instances complicated by previous dust exposure in coal mines. Table IV compares the prevalence rates found in the main groups of female pottery workers with those of women in Stoke-on-Trent who were radiographed during the same period but who had never been employed in the pottery industry. Because of the widely divergent numbers and the lower response by non-potters, the comparison is statistically not entirely satisfactory, but the evidence is at least strongly suggestive that female pottery decorators are not more liable to contract tuberculosis than other women in the area.

It is, of course, possible that the striking differences in tuberculosis rates between earthenware makers and decorators could be due to non-industrial factors, such as different living standards and housing. A study, however, of the wage structure in the Pottery Industry (1953) does not suggest any large differences between the average earnings of skilled clay workers and decorators. The poor housing conditions in Stoke-on-Trent in the past, now gradually being overcome, must have affected workers in all occupations in a similar way.

It is also noteworthy that the case finding rates in female dust tile makers were among the lowest of all female pottery workers (Table IV). Tile makers are the only group of female pottery operatives who have been subject to periodical radiographic examinations since 1939, and it seems reasonable to assume that these examinations resulted in the weeding out of elderly chronic cases and thereby lessened the risk of industrial infection. The contribution of periodical radiographic examinations towards the reduction of tuberculosis in stable industrial communities has been well shown by Fisher (1952) for the boot and shoe industry.

The high rates found in earthenware makers of both sexes and in flint workers probably reflect strongly the industrial past. The most severe risks from flint dust have now been abolished altogether, and since the war most factories have been extensively reconstructed. Many improvements in dust suppression have been introduced and in the words of the Chief Inspector of Factories (1956), "everyone has become more aware of dust risks." The pottery industry has now been chosen for a pilot investigation in industrial health.

It is, however, most unlikely that flint as a component of earthenware will be abolished altogether, and the risk from silica-containing dust will thereby remain, though in a gradually diminishing intensity. It is also worth while recalling that Gloyne (1951) found pathological evidence of active tuberculosis in 43 per cent. of pneumoconiotic potters' lungs and that in 13 per cent. of these cases the tuberculous lesions were only detected by microscopy. A considerable number of cases referred from the present investigation to chest clinics were classified as early progressive massive fibrosis and do not appear in this analysis. Some of them at least are likely to produce a positive sputum in the future and will become notified cases of tuberculosis whilst still at work.

The position will, therefore, have to be carefully watched, particularly as during the first three years of mass radiography surveys more than 25 per cent. of all operatives took no advantage of the opportunities offered to them in the

most convenient form. The controversy about the introduction of compulsory X-rays, now advocated by some epidemiologists (Lissant Cox *et al.*, 1956; Rubinstein, 1956), is outside the scope of this paper, but it seems clear that only a really comprehensive scheme of radiological supervision, at reasonably short intervals, will achieve the full control of tuberculosis in the industry.

**Summary**

1. The response by pottery operatives to Mass Radiography was 73 per cent. The acceptance rates in their relation to dust exposure, age and sex are discussed.

2. Clay workers in the earthenware industry showed significantly higher rates of tuberculosis than makers in the bone china section.

3. No significant differences in case finding rates were found between makers and decorators in the china section.

4. The prevalence of active tuberculosis in female dust tile makers was found to be low. Possible reasons for this unexpected result are discussed.

5. There are strong indications that the prevalence rates of active tuberculosis in female pottery decorators are not higher than those of women not connected with the industry.

6. The necessity for more comprehensive radiological examinations of certain groups of pottery workers is stressed.

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# THE FUNCTIONAL HYPOPITUITARISM OF ADVANCED CHRONIC PULMONARY TUBERCULOSIS

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## Introduction

The aim of this paper is to present evidence for the existence of a hypopituitary syndrome in patients with advanced chronic pulmonary tuberculosis. The existence of such a syndrome was first suspected when a patient with advanced pulmonary tuberculosis thought clinically to be suffering from Addison's disease was shown to have adrenals that responded normally to adrenocorticotrophic hormone (ACTH). This patient subsequently died, when it was found that both adrenals and pituitary gland were normal histologically. A survey of the literature suggested that such cases may have previously been described as Addison's disease, hypoadrenalism, or the low sodium syndrome. It was decided, therefore, to investigate the problem further, using standard tests of adrenal function before and after ACTH. It was not possible to make a comparable study of thyroid and gonadal functions.

## Materials and Methods

Patients were adult males and females between 30 and 75 years of age. They were selected from the following groups: advanced chronic pulmonary tuberculosis, acute pulmonary tuberculosis, and, as controls, patients with advanced lung neoplasms were chosen. With the exception of three of the patients with active tuberculosis, all the tuberculous patients were being treated with a combination of streptomycin, PAS and INAH in the usual doses. All of these patients had a positive sputum.

*Clinical:* History and routine clinical examination with special reference to wasting, blood pressure, fundal vessels and pigmentation.

*X-rays:* Routine chest X-rays, and in three patients tomographs of the adrenals and lateral films of the pituitary fossa, were taken.

*Routine tests:* Hæmoglobin (Eel photo-electric colorimeter), serum sodium and potassium (flame photometer), blood urea (urease method), plasma cholestrol (Liebman-Burchard reaction).

Eosinophil counts were made by the method of Discombe (1946) either from a finger prick or by venipuncture, the blood being collected directly or into sequestrine at about 11 a.m.

*The excretion of a water load:* This test was carried out in the standard manner, the patients not having any fluid from midnight before the test. They were instructed to empty their bladders at 7.55 a.m. and 1 litre of water

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was drunk over the next ten minutes. Urine was collected hourly for the next four hours and the volumes were measured.

*Steroid Output:* This was measured in thirty-six twenty-four-hour samples of urine collected from eighteen male patients before and after ACTH (see below). In all of these, the 17-keto-steroids were measured by both the M.R.C. (1951) and Norymbersky *et al.* methods (1953). The 17-ketogenic-steroids (Norymbersky *et al.*, 1953) were measured in fifteen patients, and the 17-hydroxycortico-steroids (Appleby *et al.* 1955) in twelve patients before and after ACTH.

*Sodium and Potassium excretion*: This was measured in twenty-four-hour specimens of urine from eighteen patients.

A sodium balance was carried out on one patient. A diet containing approximately 1 g. of NaCl was taken for four days, and on the third and fourth days urine, fæces and vomit were analysed for sodium.

*Plan of investigations:* After the routine investigations described above, a total of eighteen patients was selected from the various groups. Urine was collected from 8 p.m. on the first day to 8 p.m. on the second day. A water load test and an eosinophil count were done on the second day at 8 and 11 a.m. respectively, and at 8 p.m. 80 I.U. of " Armour " ACTH gel, or " Organon " long-acting ACTH, were injected intramuscularly. This injection was repeated at 8 p.m. on the third day. Urine was again collected from 8 p.m. on the third day to 8 p.m. on the fourth day. The water load test and eosinophil count were repeated on the morning of the fourth day. In nine of these patients the eosinophil count and water load test were repeated on the seventh day, at the same times as on the previous days, 100 m.g. of cortisone having been given orally at 6 a.m. on that day.

The blood pressure and serum sodium and potassium concentrations were recorded in a group of forty consecutive patients (male and female) admitted to two chronic tuberculosis wards.

## Results

### (1) *Functional Hypopituitarism in Patients with Advanced Tuberculosis*

In the group of patients to be described as showing functional hypopituitarism the clinical picture was of advanced chronic pulmonary tuberculosis with a poor prognosis. The patients had already received several courses of chemotherapy and prolonged hospital treatment; one of the patients (War) had not had chemotherapy for three months and was taking no drugs at the time of the investigations. The patients looked ill, were wasted and often hypotensive. The degree of wasting varied from slight in one patient (Ha, Table 1) to gross in Fa and War (Table 1). Three had symptoms of toxæmia, malaise, anorexia, etc., but were afebrile. There was increased pigmentation which was slightly more marked over pressure areas in two, and in one there was pigmentation of the lower lip. The E.S.R. ranged from 4 to 57 m.m. in one hour. One patient only had gastro-intestinal disturbances and muscle cramps. The results from these patients are presented in Table 1.

The eosinophil count was high normal or above normal in most of these patients, but this may have been related to the chemotherapy. The excretion

TABLE 1.—SUMMARISED DATA FROM A GROUP OF PATIENTS WITH ADVANCED PULMONARY TUBERCULOSIS

The first six patients have definite hypopituitarism, the seventh (Ga) has slight hypopituitarism.

| Patient | Blood pressure (mm. Hg.) | Plasma Na conc. (m.e./L.) | Plasma K conc. (m.e./L.) | Excretion of 1 litre water load (ml./4 hr.) | | Eosinophil count (per cu. mm.) | | 24-hour steroid output in mg. | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Pre-ACTH | | | | Post-ACTH | | | | | |
| | | | | Base line | After ACTH | Base line | After ACTH | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymbersky) | 17-ketogenic-steroids | 17-OH cortico-steroids | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymbersky) | 17-ketogenic-steroids | 17-OH cortico-steroids | | |
| Fa | 88 | 132 | 5·5 | 240 | 650 | 300 | 37 | 1·5 | 5·5 | — | — | 6·3 | 12·1 | — | — | | |
| Wa | 100 | 125 | 5·2 | 350 | 950 | 200 | 25 | 3·8 | 7·8 | 0·0 | 0·0 | 5·0 | 11·4 | 38·0 | 57·8 | | |
| Ed | 130 | 137 | 4·8 | 980 | 900 | 587 | 0 | 2·4 | 7·7 | 3·2 | — | 9·9 | 16·2 | 17·3 | — | | |
| Ha | 120 | 149 | 5·1 | 220 | 250 | 425 | 25 | 3·1 | 5·0 | 0·0 | 0·0 | 5·9 | 7·0 | 8·6 | 16·9 | | |
| War | 88 | 136 | 4·7 | 690 | 750 | 506 | 196 | 2·2 | 4·9 | 1·9 | 7·9 | 5·4 | 9·2 | 17·0 | 33·4 | | |
| Go | 100 | 139 | 6·2 | 980 | 840 | 81 | 356 | 5·2 | 7·2 | 0·0 | 3·1 | 24·6 | 31·4 | 24·5 | 37·2 | | |
| Ga | 130 | 143 | 5·1 | 660 | 950 | 450 | 6 | 6·5 | 7·1 | 7·3 | 5·2 | 16·8 | 13·9 | 26·8 | 26·2 | | |
| | | | | | 1,100 | | 6 | | | | | | | | | | |
| | | | | | 1,250 | | 13 | | | | | | | | | | |
| | | | | | 1,200 | | | | | | | | | | | | |

of a water load was diminished, and the twenty-four-hour output of androgenic, and in particular the gluco-corticoids, was low. The good response to ACTH indicates that the cause of the hypoadrenalism lay in pituitary hypofunction. After ACTH the eosinophil count fell significantly in most patients, and the twenty-four-hour urinary output of androgenic and gluco-corticoids rose to normal or above normal. The change in the excretion of a water load was complicated by the antidiuretic properties of the present batches of long-acting ACTH. In consequence, an enhanced or unchanged water load excretion after long-acting ACTH indicated an adrenal response (unpublished observations). A good response to ACTH was seen in this group compared with other patients. Likewise a considerable increase in water excretion was seen in two patients after cortisone (Ha and Ga, Table 1). The blood urea and plasma cholesterol was normal in all these patients. A glucose tolerance test was normal in two patients, a glucose insulin sensitivity test was normal in one patient, and showed increased sensitivity in another. Tomograms of the suprarenals and X-rays of pituitary fossæ of three of these patients were normal.

One of the patients (Fa, Table 1) died. At post-mortem examination the adrenals and pituitary were of normal size and were histologically normal. All other organs were normal and in particular there was no evidence of cirrhosis or amyloid disease.

Adrenals and pituitaries from three other patients who had died of chronic pulmonary tuberculosis, but who had not been investigated during life, were examined and found to be histologically normal. One of these patients had been hypotensive with typical Addisonian hyperpigmentation of skin. There were no pigment patches in the buccal mucosa.

### (2) *Hyponatræmia and Hypotension in Patients with Active Pulmonary Tuberculosis*

#### (*a*) *Sodium and Potassium Metabolism*

(i) The plasma sodium concentration was estimated in forty consecutive patients (twenty-five male and fifteen female) with active sputum-positive disease. In three the plasma sodium concentration was between 126 and 129 m.e./L, in five it was between 132 and 136.

There was no consistent relationship between the plasma sodium concentration and clinical state: all individuals with a low plasma sodium concentration had advanced disease, but not all patients with advanced disease had a

TABLE 2.—THE RELATIONSHIP OF SYSTEMIC BLOOD PRESSURE TO THE PLASMA SODIUM CONCENTRATION IN TWO TUBERCULOUS PATIENTS WITH HYPONATRÆMIA

Each figure is the mean of tri-weekly recordings for three weeks.

| *Subject* | *Before oral NaCl* | | *After oral NaCl* | | *Daily dose of NaCl (gm.)* |
|---|---|---|---|---|---|
| | *Plasma sodium con. m.e./L.* | *Systemic blood pressure (mm. Hg)* | *Plasma sodium con. m.e./L.* | *Systemic blood pressure (mm. Hg)* | |
| Fa | 132 | 80/60 | 149 | 100/80 | 15 |
| Wa | 130 | 130/70 | 140 | 140/80 | 7 |

lowered plasma sodium. The plasma sodium concentration was corrected in one patient and partly corrected in another by an oral supplement of sodium chloride (Table 2).

(ii) *Sodium excretion.* Patients with a low plasma sodium concentration continued to excrete appreciable quantities of sodium in their urines. This is shown in Table 3.

TABLE 3.—URINARY SODIUM CONCENTRATION AND TWENTY-FOUR-HOUR SODIUM OUTPUT FROM PATIENTS WITH ACTIVE PULMONARY TUBERCULOSIS

A considerable sodium excretion persists in patients with a low plasma sodium concentration

| *Patient* | *Plasma Na con. (m.e./L.)* | *Urinary sodium (m.e./L.)* | |
|---|---|---|---|
| | | *Concentration* | *24-hour excretion* |
| Wa .. .. .. | 126 | 96 | 74 |
| Mi .. .. .. | 129 | 26 | 44 |
| Fa .. .. .. | 132 | 96 | 110 |
| Wa .. .. .. | 136 | 122 | 144 |

In the single patient on a sodium balance (Fa, Tables 2 and 3), restriction of the sodium intake to 1 g./24 hours led to a reduction of the urinary output of sodium from 78 to 11·4 milli-equivalents per twenty-four hours. This reduction resembles, but is not as marked as, the reduction seen in normal individuals. It is clearly unlike the findings in cases of Addison's disease.

(iii) No consistent abnormalities of the plasma potassium or of potassium excretion were seen.

### (*b*) *The Blood Pressure*

Hypotension was frequently found in patients with active tuberculosis. Thirteen of forty tuberculous patients had a diastolic pressure of less than 70 mm. Hg, and eight had a systolic pressure of less than 100 mm. Hg. In five patients a normal blood pressure, and in one a slightly elevated blood pressure, accompanied retinal changes of a pre-existing hypertension. The retinal grading of these patients (Keith *et al.*, 1939) was grade II in three and grade I in three. The hypotension was found in some patients with a normal plasma sodium concentration, but patients with the lowest plasma sodium concentrations were hypotensive or showed retinal changes of pre-existing hypertension. A small but definite rise in blood pressure was seen in two patients receiving oral supplements of salt (Table 2). There appears, therefore, to be some relationship between the blood pressure and the plasma sodium concentration in these patients, but prolonged bed rest, decreased arm girth and changes in plasma volume may likewise be related.

### (3) *Acute Pulmonary Tuberculosis*

Four cases were studied and the results are presented in Table 4. In one there was early fibro-nodular disease (Ar), in one tuberculous broncho-pneumonia (Co), in one broncho-pneumonic disease with early cavitation

TABLE 4.—DATA FROM PATIENTS WITH ACUTE TUBERCULOUS DISEASE

In one, Ro, there was underlying advanced cavitating disease.

| Patient | Blood pressure (mm. Hg) | Plasma Na. conc. (m.e./L.) | Plasma K conc. (m.e./L.) | Excretion of 1 litre water load (ml./4 hr.) | | | Eosinophil count (per cu. mm.) | | | 24-hour steroid output in mg. | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Base line | After ACTH | After cortisone | Base line | After ACTH | After cortisone | Pre-ACTH | | | | | | Post-ACTH | | | | | | | |
| | | | | | | | | | | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymberský) | 17-ketogenic-steroids | 17-OH cortico-steroids | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymberský) | 17-ketogenic-steroids | 17-OH cortico-steroids | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymberský) | 17-ketogenic-steroids | 17-OH cortico-steroids |
| Ro | [illegible] | 146 | 4·7 | 390 | 110 | 830 | 425 | — | 131 | 4·2 | 5·7 | — | — | 9·8 | 13·6 | — | — | — | — | — | — | — | — |
| Co | [illegible] | 151 | 4·3 | 400 | 160 | — | 331 | 125 | — | 10·4 | 12·0 | — | — | 16·9 | 20·9 | — | — | — | — | — | — | — | — |
| Wi | [illegible] | 144 | 5·4 | 220 | 900 | 800 | 48 | 8 | 10 | 7·0 | 8·5 | 5·1 | 6·1 | 27·7 | 36·8 | 80·8 | 98·8 | — | — | — | — | — | — |
| Ar | [illegible] | 144 | 5·2 | 1,150 | 650 | — | 312 | 9 | — | 15·4 | 18·3 | 7·2 | — | 17·8 | 21·6 | 17·8 | — | — | — | — | — | — | — |

(Wi), and in one there was acute broncho-pneumonic spread from chronic cavitating disease (Ro). The initial eosinophil count was low in one patient (Wi) before chemotherapy and rose on chemotherapy. It was elevated in the two other patients already on chemotherapy. In all four there was a significant decrease in the eosinophil count after ACTH. The twenty-four-hour steroid output was slightly reduced in two patients (Ro and Wi). This may have been due to hypopituitarism associated with the underlying chronic cavitating disease in the patient Ro. In all four there was an appreciable increase in steroid output after ACTH.

The excretion of a water load has frequently been found impaired in patients with various forms of pulmonary disease in whom there was no evidence of adrenal-pituitary dysfunction (unpublished observations). The impaired water excretion shown by Co is in keeping with this finding.

### (4) *Patients with Advanced Lung Growths*

Two of the patients had a carcinoma of the bronchus proved by microscopy, one came to post-mortem: the adrenals were normal. One patient had a tumour which had blocked his left main bronchus. The histological appearances of the tumour were those of a benign fibroma. The results of the investigations in these patients are shown in Table 5. All three had an impaired excretion of a water load. It can be seen that, with the exception of Com, the change in the excretion of the water load after cortisone and ACTH did not suggest lack of these hormones. In one patient only (Com) was there significant depression of the eosinophil count after ACTH. The initial outputs of 17-keto-steroids and gluco-corticoids were low, and there was a moderate to good increase in the steroid output after ACTH. This implied hypopituitarism is at variance with the eosinophil counts and water load tests in these patients. The plasma sodium concentration and blood pressure were low-normal in one patient of this group (Com, Table 5).

## Discussion

The clinical appearance of patients with chronic advanced pulmonary tuberculosis has long been appreciated. The wasting, diffuse pigmentation and the tendency to hypotension often suggest Addison's disease. The existence of an Addison-like syndrome with normal adrenals has been reported in patients with chronic pulmonary tuberculosis (Clarke *et al.*, 1954; Sims *et al.*, 1950; Pierre-Bourgeois *et al.*, 1951). In one case only is the pituitary mentioned in the post-mortem reports (Pierre-Bourgeois *et al.*, 1951), and it was normal. Goldzieher and Edlin (1953) attributed these abnormalities of adrenocortical function to adrenal exhaustion, but did not test this hypothesis by attempting to stimulate the adrenals with ACTH. Finestone and Shuman (1951) note that the nature of the alteration in adrenal function in these patients had not been elucidated. Clark *et al.* (1954) attribute the hypoadrenalism to chronic stress from the tissue response to the tubercle bacillus.

In patients with advanced pulmonary tuberculosis the present findings of poor adrenal function from adrenals capable of a good response when stimulated with ACTH clearly places the deficiency at a pituitary level. The finding of normal pituitary histology suggests the term functional hypopituitarism. The

TABLE 5.—DATA FROM THREE PATIENTS WITH ADVANCED PRIMARY BRONCHIAL NEOPLASMS

| Patient | Blood pressure | Plasma sodium conc. (m.e./L.) | Plasma potassium conc. (m.e./L.) | 4-Hour excretion 1 litre water (ml.) | | | Eosinophil count (per cu. mm.) | | | 24-Hour urinary steroid output (mg.) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Pre-ACTH | | | | | | Post-ACTH | | | | | |
| | | | | Base line | After ACTH | After cortisone | Base line | After ACTH | After cortisone | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymberski) | 17-keto-genic-steroids | 17-OH cortico-steroids | 17-keto-steroids (M.R.C.) | 17-keto-steroids (Norymberski) | 17-ketogenic-steroids | 17-OH cortico-steroids | | | | |
| Fr | $\frac{140}{70}$ | 139 | 5·5 | 420 | 220 | 520 | 660 | 650 | — | 3·0 | 3·6 | 2·0 | 7·6 | 8·1 | 12·6 | 37·1 | 12·3 | | | | |
| Co | $\frac{170}{90}$ | 136 | 5·4 | 350 | 140 | 660 | 25 | 6 | — | 3·8 | 7·8 | 0·1 | 12·9 | 14·3 | 20·5 | 42·1 | 41·6 | | | | |
| Tr | $\frac{140}{80}$ | 145 | 4·4 | 620 | — | 520 | 50 | 75 | — | 4·8 | 8·2 | 0 | 0 | 7·3 | 14·8 | 85·0 | 30·7 | | | | |

case of a girl who developed Simmonds disease in the course of pulmonary tuberculosis (Permacchio, 1953), which recovered spontaneously when the tuberculosis was successfully treated, supports this suggestion.

There were no clinical signs of myxœdema to suggest that the production of the thyrotrophic hormone was depressed in these patients, but this point needs further investigation with radioactive iodine. However, Jauregui and Tiriodes (1954) have shown that hyperthyroidism is more common in patients with tuberculosis, and tends to regress with the tuberculosis.

The present investigations into carbohydrate metabolism are too few to be significant, but Romero and Ureta (1953) have noted the tendency for patients with pulmonary tuberculosis to have a low blood sugar.

The overall picture therefore suggests a selective hypopituitarism affecting the secretion of ACTH. This would account for the tendency to over-pigmentation in the partial hypopituitarism of tuberculosis, in contrast to the depigmentation of panhypopituitarism. In the former, the reduced circulating glucocorticoids (due to reduced ACTH secretion) and continued secretion of melanocyte-stimulating hormone (M.S.H.) would result in increased pigmentation, since gluco-corticoids depress the melanocyte-stimulating hormone (Lerner *et al.*, 1954). The assay of M.S.H. in the urines of these patients would therefore be of interest.

The possible relationship of this syndrome to inanition needs further exploration, although most of the patients studied were only moderately wasted. Hyperpigmentation may be associated with inanition as in Vagabonds' disease (Jeghars, 1944), and some authors have postulated a functional hypopituitarism in patients with anorexia nervosa (Sunderman and Rose, 1948). However, the low urinary 17-keto-steroid output in anorexia nervosa has been attributed by others to failure of the liver to conjugate this steroid (Landau *et al.*, 1948; Altschule, 1953) rather than to adrenal hypofunction. Furthermore, the excretion of a water load may be normal (Sunderman and Rose, 1948) and the urinary output of glucocorticoids is normal or high (Verney and Brown, 1947; Talbot *et al.*, 1951). The suggestion of the latter authors of a hyperadrenalism in anorexia nervosa is more in keeping with the experimental findings of adrenal hypertrophy in the starved animal (Mulinos and Pomerantz, 1941).

Sims *et al.* (1950) found that the blood urea was normal in tuberculous patients with hyponatræmia. This was confirmed in the present group of patients. This finding, together with the reduction of sodium excretion when the dietary sodium was deliberately reduced, and the normal serum K, biochemically separates the low sodium syndrome of advanced pulmonary tuberculosis from Addison's disease. It is possible, therefore, that in the former state, in contrast to Addison's disease, aldosterone secretion is unaffected. This is in keeping with the present hypothesis of a functional hypopituitarism in these patients, since ACTH does not stimulate the secretion of aldosterone (Cope and Llaurado, 1954; Venning *et al.*, 1954) which is found in normal amounts in the urine of patients with hypopituitarism (Gordon *et al.*, 1954; Luetscher and Axelrad, 1954).

The gluco-corticoid deficiency in patients with advanced chronic tuberculosis may be responsible for their well-known tendency to hyponatræmia.

This, in turn, could result in the observed hypotension. It is, therefore, tentatively proposed that the hypotension, hyponatræmia and hyperpigmentation exhibited by many of these patients may be causally related to their hypopituitarism. This hypothesis may explain the findings of Benians (1956).

There was no consistent pattern in the behaviour of the water load excretion and blood eosinophil count in the patients with primary bronchial tumours, but the steroid outputs before and after ACTH were in keeping with poor adrenal function due to hypopituitarism. The results in these patients are too few to draw any firm conclusions, although it is of interest that one of the earliest reported cases of the low sodium syndrome was in a patient with a lung neoplasm (Winkler and Crankshaw, 1938). It is possible, therefore, that the syndrome of functional hypopituitarism described here for advanced chronic pulmonary tuberculosis is common to the terminal stages of other diseases, the rapid course of which would militate against the development of the signs and symptoms of hypopituitarism, and hence its recognition. By contrast, in tuberculosis the terminal phase may last several years. Consequently, it is justifiable to speak of the functional hypopituitarism of pulmonary tuberculosis. The diagnosis may be suspected clinically, but is made ultimately on the steroid output before and after ACTH. Of the simpler tests, both the excretion of a water load before and after ACTH, and the eosinophil count and its response to ACTH, need careful interpretation; the former because of the restricted water load excretion seen in some patients with pulmonary disease, and the antidiuretic action of some batches of long-acting ACTH, and the latter because of the effect of chemotherapy.

Hypoadrenalism has been shown to affect adversely experimental tuberculosis (Steinbach, 1929; Perla and Marmorsten-Gotterman, 1933), and somatotrophic hormone appears to protect against chronic tuberculosis (Lemonide, Panisset and Selye, 1954). The improvement in the pulmonary lesions in patients with advanced chronic tuberculosis treated with ACTH (Lemaistre *et al.*, 1951; Houghton, 1954; Climie *et al.*, 1956) may therefore be due in part to correction of the postulated ACTH deficiency. That such improvement is also seen with daily ACTH in doses as small as 10-15 I.U. (Saunders-Jacobs and Shuster, unpublished observations) strongly supports this interpretation.

## Summary

I. Patients with pulmonary disease were investigated from three groups: acute tuberculosis, advanced chronic (active) tuberculosis, and primary pulmonary neoplasms.

II. No abnormalities in adrenal-pituitary function were found in two patients with acute tuberculosis, but evidence of hypopituitarism was found in one patient with underlying advanced chronic disease, and in one patient with early cavitation.

III. In three patients with advanced bronchial neoplasm, the twenty-four-hour steroid output was low, but rose considerably after ACTH. The inconsistent effect of ACTH on the eosinophil count, and of cortisone on the water load excretion, was at variance with this finding.

IV. In patients with active advanced chronic pulmonary tuberculosis

with a poor prognosis, hypotension, hyponatræmia and hyperpigmentation were frequently found. Despite the hyponatræmia, sodium output remained appreciable; and in contrast to patients with Addison's disease, dietary sodium restriction led to a very considerable reduction in the sodium output. Furthermore, there was a normal plasma concentration of urea and potassium. Some of these patients were found to have a low twenty-four-hour steroid output and reduced water load excretion. The increased steroid output and water load excretion after ACTH, together with the depression of the eosinophil count, suggested hypopituitarism. The clinical findings did not suggest panhypopituitarism, and a selective ACTH deficiency was tentatively proposed. The hyperpigmentation has been attributed to partial hypopituitarism. In view of the normal anatomy of the pituitary, the syndrome has been called the functional hypopituitarism of pulmonary tuberculosis.

This work was carried out at the Brook General Hospital, Woolwich, and I am grateful to Dr. G. E. Loxton, Dr. W. E. Mahon, Dr. R. Bruce Pearson and Dr. E. V. Saunders-Jacobs for permission to investigate patients under their care; and to the Sisters and Nursing Staff of Wards E.1 and F.1 for their co-operation. I am indebted to Dr. J. C. Thompson for steroid analyses, to Mr. D. H. Mitchell and Miss E. Packer for their assistance, and to Dr. E. N. Allott, Dr. C. L. Cope and Dr. R. Bodley Scott for criticism of the manuscript.

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# TUBERCULOSIS AND POST-GRADUATE STUDY IN VIENNA DURING THE WINTER 1890-91*

A NOTE BY F. PARKES WEBER

A PERSONAL experience of tuberculosis dating from the phenomenally cold winter of 1890-91 might be worth recording. Whilst serving as a House Physician at the Brompton Hospital in November, 1890, I happened to get a slight puncture wound into the deeper cutis vera of the terminal phalanx of the right forefinger. This bled rather freely, but I had forgotten its existence by the afternoon, when in place of the pathologist I handled a lung at the post-mortem examination on a virulent case of pulmonary tuberculosis. The slight wound on my finger healed up, but afterwards there was troublesome itching and swelling and later intermittent painful paroxysms with some local redness and flushings; there was no actual formation of pus. The little swelling was excised by Professor von Eiselsberg in Vienna in January 1891. He first regarded the lesion as a minute abscess, but afterwards, when he found no pus, was inclined to agree that it might be a small tuberculoma. Microscopic sections showed that it contained giant cells but no actual tubercle bacilli. The operation wound healed but afterwards broke down again and discharged for some time before it finally healed. A small hard scar still remains.

During the winter 1907-8 when examining patients at the Mount Vernon Hospital for Chest Diseases by the Wolff-Eisner-Calmette Ophthalmo reaction for Tuberculosis, I discovered that my own Ophthalmo-reaction was more strongly positive than that of most or all of my patients tested in the same way. In July 1916 my Pirquet cuti-reaction was strongly positive.

Although the infection in 1890 is hardly likely to have been my initial infection with tubercle bacilli, an inoculation of this kind is interesting. It occurred at the time when my general health was at its best and when my diet was as anti-tuberculous in quantity and quality as possible. It seems to me that in other cases chance infection with tubercle bacilli can seldom have occurred under circumstances more ideally favourable for the production of some degree of relative immunity. In Vienna at that time treatment of tuberculosis by Koch's old tuberculin was in vogue. The results, however, seemed to be disastrous. A kind of widespread caseous pneumonia was common. Such appearances had seldom been noted previously. There were, however, noteworthy exceptions in which the results of tuberculin treatment seemed to have been favourable. A surgeon, William Henry Bull, gave a most favourable account of such an outcome from personal experience. He had coughed up a calcified fragment and subsequently was able to continue in active practice.

* Compare F. Parkes Weber: "The Relations of Tuberculosis to General Bodily Conditions and Other Diseases." First Mitchell lecture before the Royal College of Physicians. London: H. K. Lewis and Co. 1921, 5.

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# REVIEWS OF BOOKS

*Treatment of Heart Disease.* By HARRY GROSS and ABRAHAM JEZER. New York: W. B. Saunders Company. 1956. Pp. 547.

This new volume continues the practice of explaining some clinical problems by a survey of the hæmodynamics of the circulation, with special reference to the influence of therapeutic measures on the morbid processes. This information is conveyed in a palatable fashion. Some gleanings, garnered in a rich field, are worth recording.

There is support for digitalisation in high output failure. Digitoxin, which belongs to the slow-acting group of glycosides, is widely prescribed in the United States; in Great Britain, digoxin, a quick-acting glycoside, is in common use. Embolism does not contraindicate quinidine in restoring normal rhythm from auricular fibrillation. Penicillin therapy in respiratory tract infection in children, by eliminating streptococci, much reduces the incidence of first attacks and recurrences of rheumatic fever and should be prescribed by monthly injections, or orally in daily doses until after puberty. There is no supporting evidence for salicylates as influencing the healing process. There is no uniform or satisfactory criterion for commissurotomy in the treatment of mitral stenosis; it does not cure the disease; the indications in the majority of cases are there, without resorting to cardiac catheterisation or angiocardiography. The most important measurements are the pulmonary wedge pressure, pressures in the pulmonary artery and the left atrium.

The indications for anticoagulants in myocardial infarction should be: shock, peripheral vascular disease, recurring pain in the early stages of treatment, and thromboembolic disease. Their use on a long-term basis to prevent infarction is not favoured. The widespread use of antibiotics has resulted in a reduction from 90 to 60 per cent. of positive blood cultures in subacute bacterial endocarditis. The treatment should be continuous for a month with penicillin, in large doses if necessary, and added streptomycin when required. Penicillin without bismuth has completely revised the treatment of cardiovascular syphilis, with small risk of a Herxheimer reaction; the objective is to prevent an extension of aortic damage.

T. F. COTTON.

*Clues in the Diagnosis and Treatment of Heart Disease.* By PAUL D. WHITE. Springfield Ill.: Charles C. Thomas. 1955. Pp. 186. 43 illus. $5.50.

Paul White has, throughout the years, made important contributions to our knowledge of cardiovascular diseases. This new edition is a distillate of his vast experience in this special field of medicine. When speaking in Stockholm at the European Cardiological Congress, he described himself, in an underestimate of his qualifications, as a general practitioner among specialists. He is well equipped to write this book for general practitioners, medical students, consulting physicians and cardiologists. There may be some gaps in the story he has to tell, but the essentials, with good illustrations, are all there and can be valued as axioms. Here are, chosen at random, a few clues in the diagnosis and treatment of heart disease.

Clues are found in the patient's own story and particularly in the cross-examination with respect to breathlessness, chest pain and palpitation. The signs of beginning left ventricular failure are: too easily induced dyspnœa, pulsus alternans, apical gallop rhythm, and accentuation of the pulmonary

second sound; the early right ventricular failure signs are: engorgement of the jugular veins in the sitting position, tenderness and slight enlargement of the liver, and a diastolic gallop at the lower end of the sternum. To digitalise rapidly is usually unnecessary; one contraindication is to use digitalis when it is not needed.

T. F. COTTON.

*Chronic Bronchitis.* A N.A.P.T. Symposium. 1957. Pp. 44. 6s. net.

The comprehensive study of chronic bronchitis from every possible aspect is a comparatively recent phenomenon, originating doubtless from the awakening of the leaders of the medical profession not only to the distress and suffering caused by this malady but also to its serious mortality. This short symposium cannot, and does not pretend to, do more than give readers an introduction to the work which is now being done on a really large scale in the investigation of chronic bronchitis. As such, however, it is admirable, and should provide a stimulus to careful study of the numerous articles of greater length which are now to be found in medical literature dealing with the subject. This little brochure is handy, easy to read, interesting, and important. It is strongly to be recommended.

MAURICE DAVIDSON.

*Aids to Tuberculosis Nursing.* L. E. HOUGHTON and T. HOLMES SELLORS. Fifth Edition. The Nurses' Aids Series. London: Baillière, Tindall and Cox. 8s. 6d.

This book indeed lives up to its claim to be a complete textbook of tuberculosis nursing within the limitations of its size. It gives a comprehensive view of the whole sphere of tuberculosis work, and the chapters devoted to general treatment and the sanatorium régime are excellently written. No nurse who has read this section should ever feel that tuberculosis nursing is dull and lacking in drama or human interest. The problems of prevention and the methods applied are also well presented, and there is a short chapter on the differential diagnosis of pulmonary tuberculosis which adds interest to the book as a whole.

The section on the interpretation of X-ray films, although brief, gives the nurse sufficient information to guide her through the initial stages of trying to fathom what is meant by infiltration, cavitation and fibrosis as they are shown on an X-ray film. The X-ray illustrations are not as clear as they might have been—admittedly a difficult feat in a book of this size. However, this cannot detract from the excellence of the book as a whole.

AUDREY HANSON.

*Prévention et Traitement Spécifiques de la Tuberculose par le BCG et par l'Antigène Methylique.* By LÉOPOLD NÈGRE. Paris: Masson et Cie. 1956. Pp. 242. 1,000 fr.

The appearance of another book on BCG needs some justification, and the reintroduction of a tuberculin as an immunising and therapeutic agent seems at first sight to be a nostalgic return to an era which is remembered by a decreasing number and is unknown to the majority of workers in tuberculosis. The title is to a certain extent misleading. The subject matter adds nothing to existing knowledge of BCG and is in essence an apologia for methylic antigen as an immunising and therapeutic agent. The antigen is said to

enhance the immunising action of BCG, and its combination with modern antibiotics is recommended on the ground that it fortifies their action and prolongs their therapeutic effect. Much experimental work, almost all French, is quoted. The product is obtained by extraction with pure methyl alcohol of dried young cultures of *M. tuberculosis* previously de-fatted by acetone and consists almost entirely of the phospholipids which are claimed to be the antigenic fraction of the organism. It is stated emphatically that it is not tuberculin, but it is of course *a* tuberculin. By itself it produces immunity without allergy. There is a recapitulation of much old work on the chemistry of *M. tuberculosis*. Modern work is also quoted and there is a detailed discussion of the basis of immunity in the disease. Whether or not one feels that a return to the old principles is desirable, the book leaves one in no doubt about the basic importance of active immunity. It is a stimulating, if somewhat prolix, work and it is well to be reminded that the last word on the problems of tuberculosis has not been said.

CHARLES CAMERON.

*Les Traitements Actuels des Tuberculoses Cutanées*

This monograph records the treatment of over 350 patients suffering from cutaneous tuberculosis in its varied forms seen at Lille between 1941 and 1956. It shows the progressive improvement in results as newer forms of treatment became available. The introduction of isoniazid produced great improvement and it is now extensively used in conjunction with other medicaments, Vitamin $D_2$, Streptomycin and PAS.

The clinical aspects of the various types of cutaneous tuberculosis are briefly described and the results of treatment are given in respect of each type. Five cases of cutaneous sarcoidosis are described, and in treatment of the early cases cortisone proved helpful.

An extensive bibliography is given.

P. D. SAMMAN.

*Medizinische Röntgentechnik*. By Prof. Dr. HERBERT SHOEN. Stuttgart: Georg Thieme Verlag. Pp. 347. Illus. 537.

This is the second edition of the well-known German book on radiographic technique. It deals mainly with standard radiography applied to the examination of the human skeleton and of the internal organs, and only briefly covers some of the more complex procedures.

In the description of radiographic techniques the book follows orthodox lines; the methods used are very similar to those employed in this country. One useful accessory mentioned is the well-known Shoen bridge, which has many applications; one of the most useful is that of a film holder for the examination of larger joints.

The section on the examination of the heart and lungs, and organs of the abdomen, is short and to the point. Special procedures such as bronchography and angiography are not dealt with at any length. There are no methods mentioned which are not already known and well established.

The book is profusely illustrated with clinical photographs, diagrams and radiographs, which are very helpful and simplify the understanding of the text.

It is of great credit to the author to have achieved in this short volume a concise and accurate description of most of the generally employed radio-

graphic techniques, and to have been able to include some information about special procedures which have been established as routine methods in the past few years.

R. E. STEINER.

*Die Lungentuberkulose. Diagnose und Therapie.* By P.-G. SCHMIDT. Stuttgart: Georg Thieme Verlag. 1956. Pp. xii+384. Illus. DM 58.

This is the third edition of a fine handbook on pulmonary tuberculosis, in which almost every conceivable aspect of the subject is set forth and discussed, under many headings. How thorough these descriptions and discussions are may be judged from a perusal of any one section, beginning with the first, which is an historical account of the study of the subject. This leads to the microbic causation of the disease, the " Micobacterium tuberculosis," then come the " Paths of infection," including dirty floors, sometimes soiled with particles of expectoration, and dark, damp corners, etc. Next comes " Pathological Anatomy," a subject carefully and clearly described, and accompanied by some excellent illustrations. The other numerous chapters are all equally well covered. The portions of the book dealing with the more modern methods of diagnosis and treatment will be greatly valued, including those on chemotherapy and surgical intervention.

Very important, owing to its undoubted connections with tuberculosis, is the subject of Sarcoidosis, the Besnier-Böck disease or " Lymphogranulomatosis benigna " of Schaumann (p. 158). In spite of the apparent complete absence of tubercle bacilli from local lesions, which are otherwise characteristic of tuberculosis, as well as the negative Pirquet reaction, it is generally accepted that in such cases undoubted tuberculous lesions may finally supervene. The reviewer believes that there are grounds for suggesting that all cases of Sjögren's disease, and therefore all cases of Miculicz's disease, are in some way ætiologically allied to sarcoidosis.

This book contains a stupendous amount of detailed information, and may be recommended not only to German-speaking doctors and students but to all who, though they do not speak the language, may be able to read it.

F. PARKES WEBER.

## BOOKS RECEIVED

The following books have been received and reviews of some of them will appear in subsequent issues.

*Chronic Bronchitis in Newcastle upon Tyne.* By A. G. Ogilvie and D. J. Newell. E. and S. Livingstone Ltd. Pp. 115. 15s.

*Guide Technique et Topographique d'Exploration Bronchologique.* By J. Ioannou, A. Duchet-Suchaux and A. Pinelli. Paris: Masson et Cie. Pp. 114. Illus. F. 1,400.

*La Tubercolosi di Guerra dal Punto di Vista Medico-Sociale.* Milano: Da Pensiero Medico. Pp. 14.

*La Sifilde Bronchiale.* Rome: Societa Edizioni Mediche. 1953. Pp. 78.

*Le Reinfezione Tubercolari dell' Adulto dal Punto di Vista Igienico-Sociale.* Rome: Societa Edizioni Mediche. 1953. Pp. 119.

*Come Debbono Essere Intese l'Assistenza e la Profilassi Antitubercolare nell' Infanzia.* Rome: Societa Edizioni Mediche. 1953. Pp. 99.

*Le Bronchiectasie nell' Infanzia.* Rome: Societa Edizioni Mediche. 1953. Pp. 99.

# REPORTS

*The Brompton Hospital Reports*, Vol. XXIV, 1955. London. 1957. Lloyd-Luke (Medical Books) Ltd. 15s. net.

Volume XXIV of the Brompton Hospital Reports consists of a selection from a very large number of papers published by members of the Hospital Group and the Institute of Diseases of the Chest. For anyone desiring to keep well abreast of modern research in all varieties of chest disease it will prove a valuable book of reference. In comparison with earlier publications of these Reports, this selection deals more with the scientific aspect of the diseases under discussion than with their clinical manifestations. This is perhaps inevitable in these days when the application of laboratory technique to the study of disease has had an ever-increasing stimulus; but it is to be hoped that in future editions of the Reports the publication of purely clinical articles will not be wholly neglected. This volume is conspicuous for the excellence of its illustrations, which are beautifully reproduced, and for the generous documentation of most of the articles. The editors and the publishers are to be congratulated on the production of this useful work.

## JOINT TUBERCULOSIS COUNCIL

THE Council, at its meeting on March 1, considered a report by its Radiological Committee and strongly supported the views expressed in this report, namely, that much more extensive use should be made of mass radiography and that in industry both employers and employees should—in their own interest—arrange for pre-employment X-rays and that, for the protection of the public, annual X-rays should be required of staff employed on public transport and in the catering trades.

It also recommends that the present Mass X-ray Service should be improved by providing miniature X-ray units in all chest clinics for the examination of persons referred by general practitioners, and by others who wish to have a chest X-ray. The extension of the miniature X-ray service in this way would make chest X-ray easily available for everyone, and pre-employment X-rays could be provided either by the chest clinic service or by private arrangement with industry.

## TUBERCULOSIS IN CYPRUS

### "STEADY DECREASE IN RECENT YEARS"

THE annual report of the Cyprus Medical Services, recently published in Nicosia, shows that the number of new cases of tuberculosis notified during 1955 was 187.

This was the lowest figure for the past ten years: the total in 1954 was 211 and in 1953, 251.

"Although," the report says, "notification figures cannot be fully relied upon, the steady decrease in recent years is felt to reflect an actual decline in tuberculosis morbidity in the island."

A World Health Organisation team which carried out tests in a number of villages established that the number of positive reactors to tuberculosis was very low: 4·3% in the age group 6-14 years, 15% in the group 15-19 years, 25% at 20-24 years and 37% at 25-29 years.

"If comparisons with findings in other countries are taken in respect of the

6-14 years age group, Cyprus stands at 4·3%, Denmark at 6%, S. India 10%, Egypt 35% and Mexico City 35%. From present knowledge the prevalence of tuberculosis in any area corresponds closely to the proportion of people shown to be positive reactors.

"Thus there is added support for the opinion, already held in medical circles, but not yet accepted by the population of the island at large, that the incidence of the disease is very low."

The report states that there are two sanatoria and five chest clinics in Cyprus; there is no waiting list for patients requiring sanatorium treatment and there were empty beds for most of the year at both hospitals.

## NOTES AND NOTICES

### DEATHS FROM TUBERCULOSIS AND CANCER, 1956

PROVISIONAL numbers of deaths and death rates from tuberculosis and cancer mortality in England and Wales in 1956 are announced by the Registrar-General.

#### CONTINUED FALL IN TUBERCULOSIS DEATHS

The total number of deaths from respiratory tuberculosis in 1956 was 4,851 (against 5,837 in the previous year), giving a provisional death rate of 109 per million persons. This is a decrease of 17 per cent. compared with the previous year, and means that since 1947 the death rate from respiratory tuberculosis has fallen by more than 75 per cent.

The death rate from other forms of tuberculosis was 12 per million persons, compared with 15 for 1955.

#### CANCER DEATHS AGAIN INCREASE

The provisional death rate for all forms of cancer for men was 2,274 per million population and for women 1,891; the 1955 figures were 2,252 and 1,873 respectively.

The rise in the rate for men includes an increase from 693 to 726 per million population for deaths assigned to cancer of the lung and bronchus. The rate for cancer of the lung and bronchus for women increased from 106 per million in 1955 to 111 in 1956.

Male deaths from cancer totalled 48,932, of which 15,615 or nearly 32 per cent. were certified as due to cancer of the lung and bronchus. For women, out of a total of 43,769 deaths from cancer, only 2,570 or less than 6 per cent. were ascribed to this cause. The total deaths from cancer of the lung and bronchus in males and females in 1956 were, therefore, 19,185.

### COR PULMONALE

CAMERA talks in co-operation with the Department of Medicine, University of Sheffield, have produced an interesting set of stills on "Congestive Heart Failure consequent upon Disease of the Lung." Illustrations on the "General Aspect of a Patient with Cor Pulmonale," "Cyanosis," "Jugular Venous Congestion," "Chest Disease in Cor Pulmonale," "The Bronchial Infection," "Treatment with Antibiotics and Antispasmodics," "Improving Ventilation," "The Treatment of Heart Failure," and "Maintenance Treatment," are among the subjects discussed in a well-balanced manner by the Camera Talks production.